Title

Lev**o**simendan for the **P**revention of **A**cute o**R**gan **D**ysfunction in **S**epsis: the LeoPARDS Randomised Controlled Trial.

SUPPLEMENTARY MATERIAL

END POINT MANAGEMENT

Table S1: Calculation of the SOFA core

Organ	Variable	Score 1	Score 2	Score 3	Score 4
Respiration	PaO2/FiO2 (kPa)	< 53.3	< 40	< 26.7	< 13.3
Coagulation	Platelets ($\times 10^3$ /mm^3)	< 150	< 100	< 50	< 20
Liver	Bilirubin (µmol/l)	20-32	33-101	102-204	> 204
Cardiovascular	Hypotension (all drug doses in µg/kg/min)	Mean Arterial Pressure< 70mmHg	Dopamine≤ 5 or dobutamine (any dose)	Dopamine> 5 or adrenaline≤0.1 or noradrenaline≤0.1	Dopamine> 15 or adrenaline>0.1 or noradrenaline>0.1
Central Nervous System	Glasgow Coma Score	13-14	10-12	6-9	< 6
Renal	Creatinine (µmol/l)	110-170	171-299	300-440	> 440
	Urine output (ml/day)			or UO ≤ 500	Or UO ≤ 200

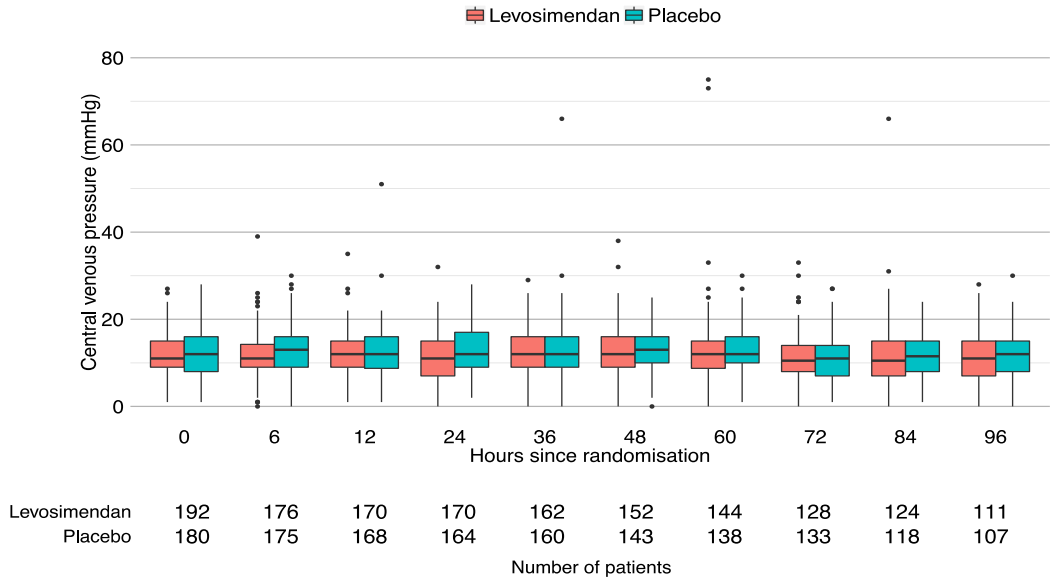
Table S2: AKIN criteria for acute renal failure classification

Criteria	Stage 1	Stage 2	Stage 3
Serum creatinine*	> 1.5-fold or ≥ 26.4 µmol/l	> 2-fold	> 3-fold or ≥ 354 µmol/l if acute rise from baseline ≥ 44 µmol/l
Urine output	< 0.5ml/kg/hr for 6 hrs+	< 0.5ml/kg/hr for 12 hrs+	< 0.3ml/kg/hr for 24 hrs+ or or 0mls for 12hrs+
RRT†	No	No	Yes

*increase from baseline unless otherwise stated; † RRT=Renal replacement therapy

BASELINE DATA

LONGITUDINAL MEASUREMENTS



Line = median, box = interquartile range, whiskers = extremes of the data (x1.5 the interquartile range) and circles = very extreme outliers. The data shown include patients still living and still in ICU for each time point since randomization.

Figure S1: Box plot for central venous pressure by treatment group

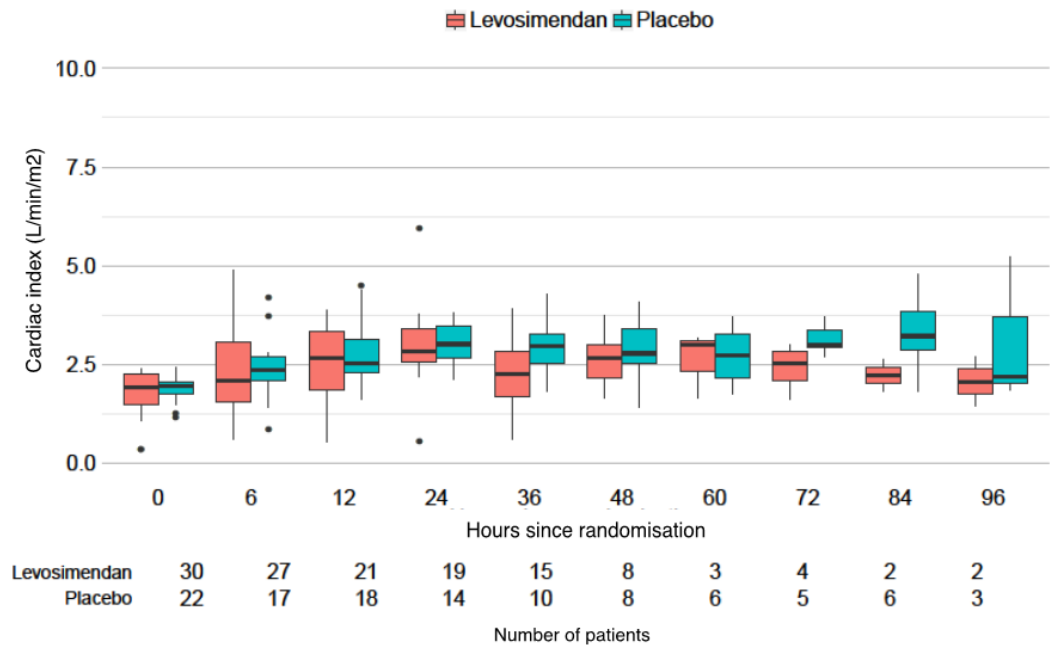


Figure S2: Box plot for cardiac index by treatment group, in patients in the lowest tertile for baseline cardiac index (≤ 2.44 L/min/m2)

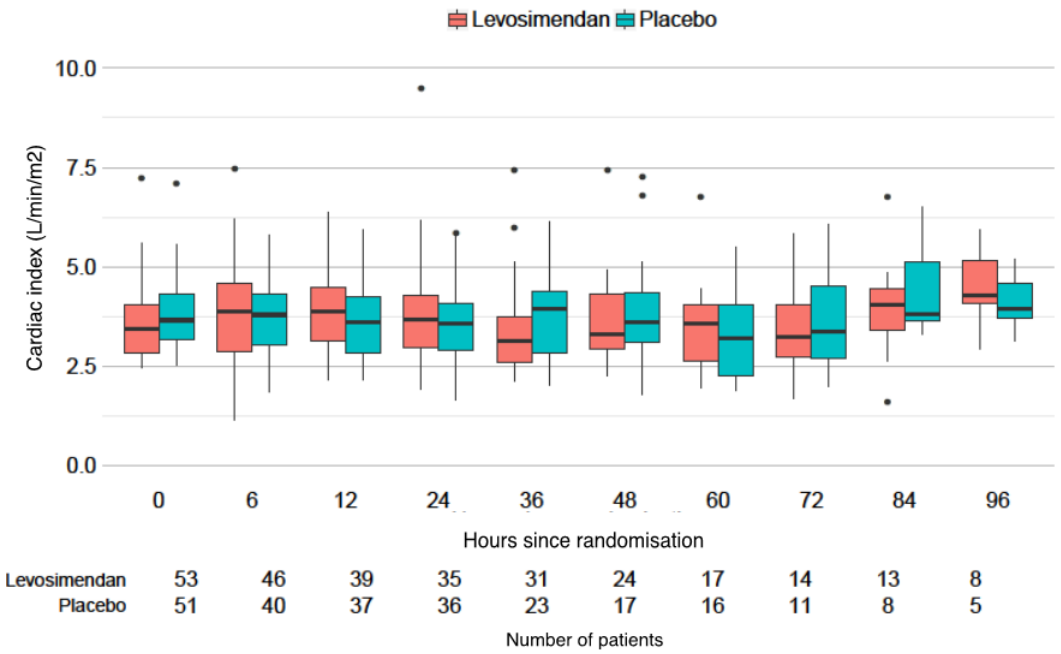


Figure S3: Box plot for cardiac index by treatment group, in patients in the middle and highest tertiles for baseline cardiac index combined (> 2.44 L/min/m2)

Table S3: Number of patients with serious adverse events, intention to treat basis

	Levosimendan n(%)	Placebo n(%)	Difference*
Life threatening arrhythmias	15 (5.8)	6 (2.3)	3.5 (-0.3,7.3)
Atrial fibrillation/ Supraventricular tachycardia	8 (3.1)	1 (0.4)	2.7 (0.1,5.3)
Bradycardia	0 (0.0)	2 (0.8)	-0.8 (-2.2,0.7)
Ventricular fibrillation/ ventricular tachycardia	7 (2.7)	3 (1.2)	1.5 (-1.2,4.3)
Myocardial infarction/ acute coronary syndrome	3 (1.2)	1 (0.4)	0.8 (-1.1,2.7)
Other	18 (7.0)	17 (6.6)	0.4 (-4.3,5.1)
Total†	32 (12.4)	23 (8.9)	3.5 (-2.3,9.2)

Patients with multiple SAEs in one category are counted only once

*Absolute difference Levosimendan – Placebo

†Patients with multiple SAEs are counted only once

Table S4: Number of patients with serious adverse events by organ system, intention to treat basis

	Levosimendan n(%)	Placebo n(%)	Difference*
Cardiovascular/circulatory	22(8.5)	10 (3.9)	4.6 (0.1,9.2)
Digestive/GI	6 (2.3)	7 (2.7)	-0.4 (-3.5,2.7)
Nervous system	2 (0.8)	3 (1.2)	-0.4 (-2.5,1.7)
Respiratory	5 (1.9)	3 (1.2)	0.8 (-1.8,3.3)
Total†	32 (12.4)	23 (8.9)	3.5 (-2.3,9.2)

Patients with multiple SAEs in one category are counted only once. There were no patients with SAEs in the urinary/excretory, musculo-skeletal or skin/hair/nails organ systems.

*Absolute difference Levosimendan – Placebo

†Patients with multiple SAEs are counted only once

Table S5: Number of adverse events by SAE classification and relationship to study medication, as treated basis

		Number of AEs†		Number of subjects‡	
Classification	Relationship*	Levosimendan	Placebo	Levosimendan	Placebo
Not serious	Definite	1	0	1	0
	Not assessable	0	1	0	1
	Not related	26	12	7	4
	Possible	24	16	19	13
	Probable	6	0	5	0
	Unlikely	16	16	8	10
Serious	Definite	0	0	0	0
	Not assessable	0	0	0	0
	Not related	9	11	8	10
	Possible	15	3	12	1
	Probable	1	0	1	0
	Unlikely	13	10	11	10
Total	all	111	69	72	49

Multiple entries for the same adverse event are only counted once (according to most serious classification and highest level of causality)

†A subject may have more than one adverse event

‡A subject is only shown once, using their adverse event with the most serious classification and highest level of causality

Table S6: Number of patients with serious adverse events, as treated basis

	Levosimendan n(%)	Placebo n(%)	Difference*
Life threatening arrhythmias	15 (5.8)	5 (2.0)	3.9 (-0.2,7.7)
Atrial fibrillation/ Supraventricular tachycardia	8 (3.1)	1 (0.4)	2.7 (0.1,5.4)
Bradycardia	0 (0.0)	2 (0.8)	-0.8 (-2.3,0.7)
Ventricular fibrillation/ ventricular tachycardia	7 (2.7)	2 (0.8)	2.0 (-0.7,4.6)
Myocardial infarction/ acute coronary syndrome	3 (1.2)	1 (0.4)	0.8 (-1.1,2.7)
Other	18 (7.1)	17 (6.7)	0.3 (-4.4,5.1)
Total†	32 (12.5)	22 (8.7)	3.9 (-1.9,9.6)

Patients with multiple SAEs in one category are counted only once

*Absolute difference Levosimendan – Placebo

†Patients with multiple SAEs are counted only once

SECONDARY OUTCOMES

Cardiovascular

There were 203/515 (39%) patients who had cardiac output measured at least once post-randomisation. Table S7 compares baseline characteristics for those patients with at least one cardiac output measurement post-randomisation and those without. Patients who had cardiac output measurements recorded after baseline were sicker (higher APACHE II scores and requiring more organ support), had more cardiac comorbidities and were receiving higher doses of noradrenaline at baseline. Box plots of $ScvO_2$ and cardiac index by treatment group are shown in figures 6 and 7 in section 4.4.2, along with the number of patients with measurements at each time point.

Table S8 shows the effect of levosimendan on cardiac index and $ScvO_2$ based on regression models. The models adjusted for any baseline differences and allowed for similarity between adjacent time points using a random walk process. For cardiac index the correlation of measurements within patient was modelled using patient-level random intercept term. The same model did not converge for $ScvO_2$ so we present the results without the patient random effects, acknowledging that the credible intervals may be too narrow. Treatment differences are expressed as a ratio comparing levosimendan and placebo at each time point, and averaged over all time points taking the geometric mean (due to the log transform applied to the cardiovascular measures). We also express the treatment difference as the difference in the areas under the curves on the log scale as specified in the SAP.

Cardiac index values were higher in the levosimendan group at all time points except 36 hours, though 95% credible intervals include 1. There was no consistent pattern over the 96 hours, though the largest differences were seen within the 24 hour period post-randomisation while levosimendan was being administered. Similarly, the average treatment ratio and difference in areas are positive, indicating higher values in levosimendan patients, though the 95% credible intervals are wide and consistent with no effect.

$ScvO_2$ showed a consistent pattern over time, though the uncertainty may be underestimated because within-patient correlations were not accounted for. We therefore fitted a regression model including patient random effects but without the treatment-time interaction, enabling convergence. This yielded a treatment ratio of 1.03 (1.01, 1.04) (constant over time as there was no treatment-time interaction), similar to the average treatment ratio shown in table S8.

Table S7: Baseline characteristics of those with and without cardiac output (CO) measurements.

Values are median (lower quartile, upper quartile) for continuous variables and n (%) for dichotomous and categorical variables

	No CO measurements (after baseline) n=312	Some CO measurements (after baseline) n=203	All patients n =515
Age (years)	68 (58,76)	68 (59,76)	68 (58,76)
Gender (male)	162 (51.9)	127 (62.6)	289 (56.1)
Weight (kg)	79 (65,91)	77 (66,89)	79 (66,90)
BMI (kg/m^2)	28 (23,32)	26 (23,30)	27 (23,31)
Ethnicity			
Asian	12 (3.8)	9 (4.4)	21 (4.1)
Black	3 (1)	7 (3.4)	10 (1.9)
Caucasian	295 (94.6)	185 (91.1)	480 (93.2)
Other	2 (0.6)	2 (1)	4 (0.8)
Recent surgical history	104 (33.3)	85 (41.9)	189 (36.7)
APACHE II score	24 (21,30)	26 (22,32)	25 (21,30)
Pre-existing conditions			
Ischemic Heart Disease	42 (13.5)	35 (17.2)	77 (15)
Congestive Heart Failure	3 (1)	2 (1)	5 (1)

Cardiac Failure	20 (6.4)	29 (14.3)	49 (9.5)
Severe COPD	14 (4.5)	13 (6.4)	27 (5.2)
Chronic Renal Failure	27 (8.7)	10 (4.9)	37 (7.2)
Cirrhosis	4 (1.3)	6 (3)	10 (1.9)
Immunocompromised	26 (8.3)	21 (10.3)	47 (9.1)
Diabetes	66 (21.2)	44 (21.7)	110 (21.4)
Beta-blockers normally taken	64 (20.5)	35 (17.2)	99 (19.2)
Organ failure			
Respiratory	112 (36)	88 (43.6)	200 (39)
Renal	78 (25.1)	73 (36)	151 (29.4)
Liver	8 (2.6)	6 (3)	14 (2.8)
Haematological	18 (5.8)	11 (5.5)	29 (5.7)
Neurological	133 (47.3)	95 (61.3)	228 (52.3)
SOFA score	10 (8,12)	11 (9,13)	10 (8,12)
Source of infection			
Lung	124 (39.9)	77 (37.9)	201 (39.1)
Abdomen	104 (33.4)	87 (42.9)	191 (37.2)
Urine	21 (6.8)	8 (3.9)	29 (5.6)
Primary bacteraemia	5 (1.6)	5 (2.5)	10 (1.9)
Neurological	4 (1.3)	1 (0.5)	5 (1)
Soft tissue or line	17 (5.5)	9 (4.4)	26 (5.1)
Other	36 (11.6)	16 (7.9)	52 (10.1)
Positive culture	143 (46)	78 (38.4)	221 (43)
Mechanical ventilation	233 (74.7)	184 (90.6)	417 (81)
Renal Replacement therapy	42 (13.5)	47 (23.2)	89 (17.3)
Moderate or severe ARDS	65 (20.8)	66 (32.5)	131 (25.4)
Heart Rhythm			
Sinus rhythm	257 (82.4)	162 (80.6)	419 (81.7)
Atrial fibrillation	32 (10.3)	21 (10.4)	53 (10.3)

Paced	1 (0.3)	4 (2)	5 (1)
Other irregular rhythm	22 (7.1)	14 (7)	36 (7)
Physiological variables			
Mean Arterial Pressure (mmHg)	75 (69,80)	72 (66,78)	74 (68,79)
Heart Rate (beats/min)	94 (80,110)	98 (82,112)	95 (80,110)
Central venous pressure (mmHg)	11 (8,15)	12 (9,15)	11 (8,15)
Cardiac output (L/min)	6 (4,8)	6 (4,8)	6 (4,8)
Cardiac index ($L/min/m^2$)	3.4 (2,3.9)	2.9 (2.2,3.8)	3 (2.2,3.8)
SaO_2 (%)	97 (95,98)	97 (95,98)	97 (95,98)
$ScvO_2$ (%)	75 (68,80)	77 (70,81)	76 (69,81)
Lactate (mmol/l)	2.1 (1.3,3.3)	2.5 (1.7,4.5)	2.3 (1.4,3.6)
PaO_2/FiO_2 (kPa)	29 (21,41)	28 (19,36)	29 (20,39)
Creatinine (µmol/l)	130 (84,198)	151 (105,232)	138 (91,213)
Bilirubin (µmol/l)	14 (8,24)	15 (9,29)	14 (8,26)
Hb (g/l)	108 (92,122)	108 (94,126)	108 (94,124)
Platelets ($x10^9/l$)	212 (141,307)	216 (138,304)	215 (140,307)
GCS	10 (3,15)	3 (3,15)	9 (3,15)
Volume of IV fluid in last 4 hours (mls)	686 (432,1077)	857 (464,1348)	738 (442,1206)
Time from shock to randomisation (hrs)	14 (10,20)	17 (12,22)	16 (10,21)
Vasoactive drugs at randomisation			
Noradrenaline			
No. of patients (%)	310 (99.4)	198 (97.5)	508 (98.6)
Median (IQR) dose (µg/kg/min)	0.24 (0.14,0.42)	0.36 (0.21,0.53)	0.28 (0.16,0.47)

Adrenaline			
No. of patients (%)	20 (6.4)	22 (10.8)	42 (8.2)
Median (IQR) dose (µg/kg/min)	0.14 (0.07,0.25)	0.12 (0.08,0.36)	0.14 (0.07,0.3)
Vasopressin			
No. of patients (%)	31 (9.9)	39 (19.2)	70 (13.6)
Median (IQR) dose (Units/min)	0.04 (0.03,0.04)	0.02 (0.02,0.03)	0.03 (0.02,0.04)
Terlipressin			
No. of patients (%)	2 (0.6)	3 (1.5)	5 (1)
Median (IQR) dose µg/kg/min)	1.40 (0.71,2.09)	0.02 (0.01,0.02)	0.02 (0.02,0.03)
Dobutamine			
No. of patients (%)	16 (5.1)	24 (11.8)	40 (7.8)
Median (IQR) dose (µg/kg/min)	5 (4.4,7.1)	5.40 (4.5,6.4)	5.20 (4.4,6.5)
GTN			
No. of patients (%)	1 (0.3)	1 (0.5)	2 (0.4)
Median (IQR) dose (mg/hr)	1 (1,1)	0.50 (0.5,0.5)	0.80 (0.6,0.9)

Table S8: Estimated effect of levosimendan on cardiovascular measures from regression models

	Cardiac index	$ScvO_2$*
Treatment ratio for Levosimedan vs Placebo (95% CrI) at:		
6 hours	1.05 (0.97,1.14)	1.03 (1.02,1.04)
12 hours	1.09 (1.00,1.19)	1.03 (1.01,1.04)
24 hours	1.07 (0.98,1.17)	1.03 (1.02,1.04)
36 hours	0.99 (0.89,1.09)	1.03 (1.01,1.04)
48 hours	1.03 (0.93,1.13)	1.02 (1.01,1.04)
60 hours	1.05 (0.95,1.16)	1.02 (1.01,1.04)
72 hours	1.03 (0.92,1.13)	1.03 (1.02,1.05)
84 hours	1.06 (0.95,1.18)	1.03 (1.01,1.05)
96 hours	1.06 (0.95,1.19)	1.03 (1.01,1.04)
Average treatment ratio†	1.05 (0.97,1.13)	1.03 (1.02,1.04)
Difference in area under curve (log scale)	3.91(-2.85,10.70)	2.43(1.67,3.17)

* Patient random effects not included due to convergence problems; † Geometric mean; CrI=credible interval

Renal

Renal failure on day 14

Renal failure on day 14 was missing for ten patients, six of whom were discharged on day 14 or 15. Of the remaining four patients, three had scores of zero before and after day 14 and one had a score of zero before and one after. As with the primary outcome, last observation carried forward was used to impute all values.

The cumulative logistic models compared the odds of being in or above a particular renal failure category for Levosimendan versus Placebo. As described in section 3.10.6 we chose a constrained proportional odds model with a common treatment effect for renal failure stages 1 to 3, and a separate effect for death. The results are presented in tables S9 (unadjusted) and S10 (adjusted for age and APACHE II score). The constrained proportional odds model gave an OR (95% CI) for renal failure stages 1 to 3 comparing levosimendan to

placebo as 1.37 (0.96, 1.95). The odds ratio for death was 1.19 (0.81,1.73). Alternative models with proportional odds for all stages (a simpler model), and non-proportional odds for all stages (a more complex model) are also presented; the deviance showed there was little difference between the models. Adjustment for age and APACHE II score gave slightly higher odds ratio for renal failure.

Table S9: Unadjusted cumulative odds models for renal failure at day 14

<table>
<tr><th></th><th>Proportional odds</th><th>Non-proportional odds</th><th>Constrained proportional odds</th></tr>
<tr><td>Treatment OR for RF> stage 1*</td><td rowspan="4">1.32 (0.93,1.86)</td><td>1.36 (0.95,1.93)</td><td rowspan="3">1.37 (0.96,1.95)</td></tr>
<tr><td>Treatment OR for RF> stage 2*</td><td>1.34 (0.94,1.92)</td></tr>
<tr><td>Treatment OR for RF> stage 3*</td><td>1.40 (0.97,2.02)</td></tr>
<tr><td>Treatment OR for RF> stage 4*</td><td>1.21 (0.82,1.78)</td><td>1.19 (0.81,1.73)</td></tr>
<tr><td>Deviance</td><td>1035.70</td><td>1033.30</td><td>1033.90</td></tr>
<tr><td>Residual degrees of freedom</td><td>2055</td><td>2052</td><td>2054</td></tr>
</table>

* Odds ratio comparing Levosimendan and placebo with 95% confidence interval

Table S10: Adjusted cumulative odds models for renal failure at day 14

	Proportional odds	Non-proportional odds	Constrained proportional odds
Treatment OR for RF> stage 1*	1.36 (0.94,1.96)	1.42 (0.97,2.08)	1.43 (0.99,2.09)
Treatment OR for RF> stage 2*		1.40 (0.95,2.05)	
Treatment OR for RF> stage 3*		1.46 (0.99,2.15)	
Treatment OR for RF> stage 4*		1.22 (0.81,1.84)	1.20 (0.80,1.79)
Age (years)	1.01 (1.00,1.03)	1.01 (1.00,1.03)	1.01 (1.00,1.03)
APACHE II	1.12 (1.09,1.15)	1.12 (1.09,1.15)	1.12 (1.09,1.15)
Deviance	959.50	956.80	957.40
Residual degrees of freedom	2053	2050	2052

* Odds ratio comparing Levosimendan and placebo with 95% confidence interval

Renal replacement therapy

Duration of renal replacement therapy (RRT) was defined as the first day of RRT in ICU to the last day of RRT, including any RRT received post-discharge. All days in between were counted, whether or not the patient received RRT on each day.

Table S11: Duration of renal replacement therapy from first to last day

	Levosimendan		Placebo		Difference (95% CI)*
No RRT, n(%)	156	(60.5)	155	(60.3)	0.2 (-8.3,8.6)
Median (lq,uq) duration RRT (all patients)	0.0	(0,2)	0.0	(0,3)	0.0 (0.0,0.0)
Median (lq,uq) duration RRT (some RRT)	3.0	(1,8)	5.0	(2,9)	-2.0 (-3.0,0.0)

* Absolute difference in proportions Levosimendan – Placebo; median difference calculated using bootstrap

Respiratory

Ventilator Free days

There was no difference in the distribution of ventilator free days between treatment groups from the Mann-Whitney test (p=0.14).

Table S12: Ventilator free days

	Levosimendan		Placebo		Difference (95% CI)
No days free, n(%)	88	(34.38)	72	(28.46)	5.92 (-2.13,13.96)
28 days free, n(%)	30	(11.72)	30	(11.86)	-0.14 (-5.74,5.46)
Median (lq,uq) days free	16	(0,25)	19	(0,25)	-3.00 (-9.50,1.00)

* Absolute difference in proportions Levosimendan – Placebo; median difference calculated using bootstrap

PaO_2/FiO_2 ratio

Box plots of PaO_2/FiO_2 ratio by treatment group over time were shown in figure 13 in section 4.4.2. These plots, along with individual patient trajectories, did not indicate departures from linearity, though measurements were highly variable within individuals. PaO_2/FiO_2 ratio would be expected to be recorded for every day the patient is ventilated and on ICU. PaO_2/FiO_2 ratio was missing for 6% (219/3675) of patient-days where the patient

was on the ventilator. As with the primary outcome, last observation carried forward was used to impute all values.

Table S13 shows the main results for the full model as described above, along with planned sensitivity analysis. The PaO_2/FiO_2 ratio was lower in the levosimendan patients on day 1 (mean treatment difference -2.19 [-3.63, -0.74]). The PaO_2/FiO_2 ratio was higher in the levosimendan patients on days 7 (the duration levosimendan or its metabolite are active) and day 9 (median length of stay in survivors) though 95% credible intervals were wide and crossed zero. The mean change per day was higher in levosimendan patients (1.23 [0.95, 1.53]) kPa per day compared to 0.77 (0.50, 1.05) kPa in placebo patients, with the probability of faster improvement in levosimendan patients exceeding 99%. Restricting the data to shorter timescales resulted in a lower estimated change per day in PaO_2/FiO_2 ratio in both treatment arms, though the probability of faster increases in the levosimendan arm remained over 0.9. Treatment differences were similar after adjusting for age and APACHE II score, and for ICU effects. More detailed results, along with results for alternative joint models, can be found in the Report Supplementary Material. Simpler models which did not fully acknowledge the relationship between the survival and longitudinal models gave a poorer fit to the data.

Table S13: Estimated effects of levosimendan on PaO2/FiO2 ratio from joint longitudinal and survival models

	Full model	7 days	14 days	21 days	Age and APACHE II	ICU effects
Change in PaO_2/FiO_2 per day – Levosimendan, kPa (95% CrI)	1.23 (0.95,1.53)	0.85 (0.47,1.25)	0.93 (0.62,1.25)	1.09 (0.80,1.40)	1.23 (0.95,1.52)	1.23 (0.95,1.53)
Change in PaO_2/FiO_2 per day – Placebo, kPa (95% CrI)	0.77 (0.50,1.05)	0.38 (0.00,0.77)	0.65 (0.34,0.96)	0.78 (0.49,1.08)	0.77 (0.50,1.04)	0.77 (0.50,1.05)
Probability of faster improvement in Levosimendan group	0.996	0.955	0.910	0.946	0.996	0.995
Treatment difference in	-2.19 (-3.63,-0.74)	-2.43 (-3.90,-0.98)	-2.00 (-3.47,-0.49)	-2.18 (-3.67,-0.75)	-2.13 (-3.59,-0.70)	-2.21 (-3.64,-0.75)

PaO_2/FiO_2 on day 1, kPa (95% CrI)						
Treatment difference in PaO_2/FiO_2on day 7, kPa (95% CrI)	1.06 (-1.57,3.70)	0.86 (-2.85,4.64)	-0.01 (-3.05,2.96)	0.00 (-2.78,2.81)	1.13 (-1.47,3.73)	1.03 (-1.59,3.62)
Treatment difference in PaO_2/FiO_2 on day 9, kPa (95% CrI)	1.98 (-1.26,5.23)	1.80 (-2.91,6.61)	0.56 (-3.25,4.28)	0.63 (-2.82,4.10)	2.06 (-1.15,5.26)	1.95 (-1.27,5.13)

Treatment difference is levosimendan compared to placebo

TIME TO EXTUBATION

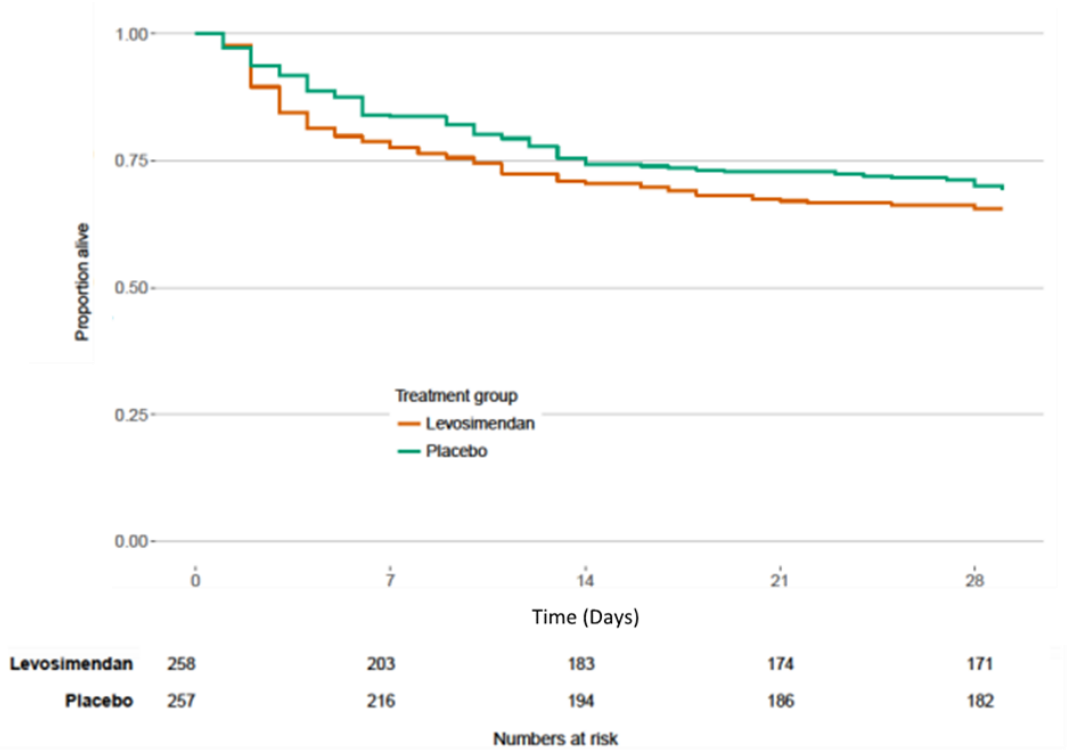


Figure S4: Kaplan-Meier plot for survival to 28 days

Table S14: Survival by treatment group

	Levosimendan	Placebo	Difference (95% CI)*
28 day mortality, n(%)	89 (34.50)	79 (30.86)	3.64 (-4.47,11.74)
ICU mortality, n(%)	83 (32.17)	76 (29.57)	2.60 (-5.38,10.57)
Hospital mortality, n(%)	97 (37.60)	84 (32.81)	4.78 (-3.46,13.03)
3 month mortality, n(%)	100 (38.91)	91 (35.69)	3.22 (-5.15,11.60)
6 month mortality, n(%)	105 (40.86)	98 (38.43)	2.42 (-6.05,10.90)

* Absolute difference in proportions Levosimendan – Placebo

Table S15: Cox regression for survival to 28 days

	Unadjusted	Adjusted
Treatment difference*	1.19 (0.88,1.61)	1.24 (0.91,1.67)
Age (years)		1.02 (1.00,1.03)
APACHE II		1.09 (1.06,1.11)

*Hazard ratio comparing Levosimendan to Placebo; adjusted analysis includes random effects for ICU

Table S16: Cox regression for survival to 6 months

	Unadjusted	Adjusted
Treatment difference*	1.12 (0.85,1.47)	1.15 (0.87,1.51)
Age (years)		1.02 (1.00,1.03)
APACHE II		1.09 (1.06,1.11)

*Hazard ratio comparing Levosimendan to Placebo; adjusted analysis includes random effects for ICU

Liver

Box plots of bilirubin by treatment group over time were shown on the log scale in figure 9 in section 4.4.2. These plots, along with individual patient trajectories, did not indicate departures from linearity. Bilirubin was missing for 13% (706/5355) of patient-days in ICU. As with the primary outcome, last observation carried forward was used to impute all values.

As the outcome variable is log transformed, to express changes on a clinically meaningful scale the regression parameters were exponentiated to give a ratio. Table S17 shows results for the full model, along with planned sensitivity analysis. Bilirubin was similar in the levosimendan and placebo patients on day 1 (mean treatment difference comparing levosimendan to placebo 4% [-6, 14]). The difference increased to 24% (6,46) on day 7 and to 31% (8,59) on day 9. Bilirubin decreased over time, with the mean reduction per day smaller in levosimendan patients (-5% [-6,-3]) compared to placebo patients (-7% [-8,-6]), with the probability of faster reduction in levosimendan patients being 0.4%. Restricting the data to shorter timescales resulted in smaller treatment differences between levosimendan and placebo arms, with 95% credible intervals including zero. Treatment differences were similar after adjusting for age and APACHE II score, and for ICU effects. More detailed results, along with results for alternative joint models, can be found in the Supplementary Material. As with the models for PaO_2/FiO_2 ratio, simpler models which did not fully acknowledge the relationship between the survival and longitudinal models gave a poorer fit to the data.

Table S17: Estimated effects of levosimendan on bilirubin from joint longitudinal and survival models;

All differences expressed as ratios due to log transformation

	Full model	7 days	14 days	21 days	Age and APACHE II	ICU effects
Change in bilirubin ration per day - Levosimendan (95% CrI)	0.95 (0.94,0.97)	0.96 (0.94,0.98)	0.96 (0.94,0.97)	0.96 (0.94,0.97)	0.95 (0.94,0.97)	0.95 (0.94,0.97)
Change in bilirubin ratio per day - Placebo (95% CrI)	0.93 (0.92,0.94)	0.96 (0.94,0.98)	0.95 (0.93,0.96)	0.94 (0.92,0.95)	0.93 (0.91,0.94)	0.93 (0.92,0.95)
Probability of faster reduction in Levosimendan group	0.004	0.324	0.190	0.030	0.006	0.011
Treatment difference in bilirubin on day 1 (95% CrI)	1.04 (0.94,1.14)	1.05 (0.96,1.15)	1.04 (0.94,1.15)	1.04 (0.94,1.14)	1.03 (0.94,1.14)	1.04 (0.94,1.14)
Treatment difference in bilirubin on day 7 (95% CrI)	1.24 (1.06,1.46)	1.11 (0.89,1.35)	1.13 (0.94,1.37)	1.21 (1.01,1.42)	1.24 (1.06,1.45)	1.24 (1.05,1.46)

Treatment difference in bilirubin on day 9 (95% CrI)	1.31 (1.08,1.59)	1.12 (0.85,1.45)	1.16 (0.92,1.47)	1.26 (1.02,1.54)	1.31 (1.08,1.58)	1.31 (1.06,1.59)

Treatment difference is levosimendan compared to placebo

Major Acute Kidney Events by Day 28 (MAKE28)

Table S18: MAKE28 by treatment group

	Levosimendan		Placebo		Difference (95% CI)
MAKE28, n(%)	148	(57.4)	139	(54.3)	3.1 (-5.5,11.6)
Death	89	(34.5)	79	(30.9)	3.6 (-4.5,11.7)
RRT	62	(24.1)	62	(24.1)	0.0 (-7.4,7.4)
Prolonged RF	118	(45.7)	108	(42.0)	3.7 (-4.9,12.3)

Table S19: Logistic regression analysis for MAKE28

	Odds ratios (95% CI)
Treatment difference*	-0.15 (-0.52, 0.22)
Age†	0.19 (0.00, 0.38)
APACHE II†	0.69 (0.49, 0.91)

* Levosimendan compared to placebo

†Variables were standardised so Odds ratios correspond to a 1SD increase

OTHER SECONDARY OUTCOMES

ICU-free days

There was no evidence of a difference in ICU free days between treatment groups from the Mann-Whitney test (p=0.11).

Table S20: ICU free days

	Levosimendan	Placebo	Difference (95% CI)
No days free, n(%)	107.00 (41.47)	90.00 (35.16)	6.32 (-2.07,14.70)
Median (lq,uq) days free	10.50 (0,20)	14.00 (0,21)	-3.50 (-10.50,1.00)

* Absolute difference in proportions Levosimendan – Placebo; median difference calculated using bootstrap

Days free of catecholamine therapy

Table S21: Catecholamine free days

	Levosimendan	Placebo	Difference (95% CI)
No days free, n(%)	90.00 (34.88)	79.00 (30.86)	4.02 (-4.09,12.14)
Median (lq,uq) days free	22.00 (0,26)	23.00 (0,26)	-1.00 (-4.50,1.00)

* Absolute difference in proportions Levosimendan – Placebo; median difference calculated using bootstrap

Length of stay

Note that length of stay starts at admission which precedes randomisation, therefore subjects who died within 28 days of follow up may have a length of stay exceeding 28 days.

Table S22: ICU length of stay

	Levosimendan	Placebo	Total
Survived to ICU discharge	9.1 (5,16.1)	9.0 (4.9,14.1)	9.1 (4.9,15.1)
Died in ICU	3.2 (1.4,8.9)	5.7 (2.2,11.7)	4.3 (1.5,10.3)
All patients	7.3 (3.2,14.8)	8.3 (3.9,13.5)	7.9 (3.5,14)

Median (lower quartile, upper quartile)

Table S23: Hospital length of stay

	Levosimendan	Placebo	Total
Survived to hospital	30.1 (16.8,48)	27.7 (18,52.3)	29 (17.3, 49.3)
Died in hospital	8.2 (3.4,18.6)	11.3 (5.1,25.7)	9.4 (3.7,21.1)
All patients	19.6 (10.1,40.4)	22.7 (11.7,42.3)	21.5 (10.9,41.6)

Median (lower quartile, upper quartile)

Two patients were excluded as they were still in hospital at the time of locking the trial database.

Organ support days

Table S24: Organ support days as defined by the Critical Care Minimum Dataset

	Levosimendan	Placebo	Total
Advanced respiratory support days	4.0 (2,10)	5.0 (2,9)	4.0 (2,10)
Basic respiratory support days	1.0 (0,3)	1.0 (0,3)	1.0 (0,3)
Advanced cardiovascular support	2.0 (1,4)	2.0 (1,4)	2.0 (1,4)
Basic cardiovascular support days	4.5 (1,10)	5.0 (2,10)	5.0 (2,10)
Renal support days	0.0 (0,2)	0.0 (0,4)	0.0 (0,3)
Neurological support days	0.0 (0,0)	0.0 (0,0)	0.0 (0,0)
Gastrointestinal support days	5.0 (0,12.8)	6.0 (0.5,11)	5.0 (0,11)
Dermatological support days	0.0 (0,0)	0.0 (0,0)	0.0 (0,0)
Liver support days	0.0 (0,0)	0.0 (0,0)	0.0 (0,0)

Median (lower quartile, upper quartile)

BIOMARKER DATA

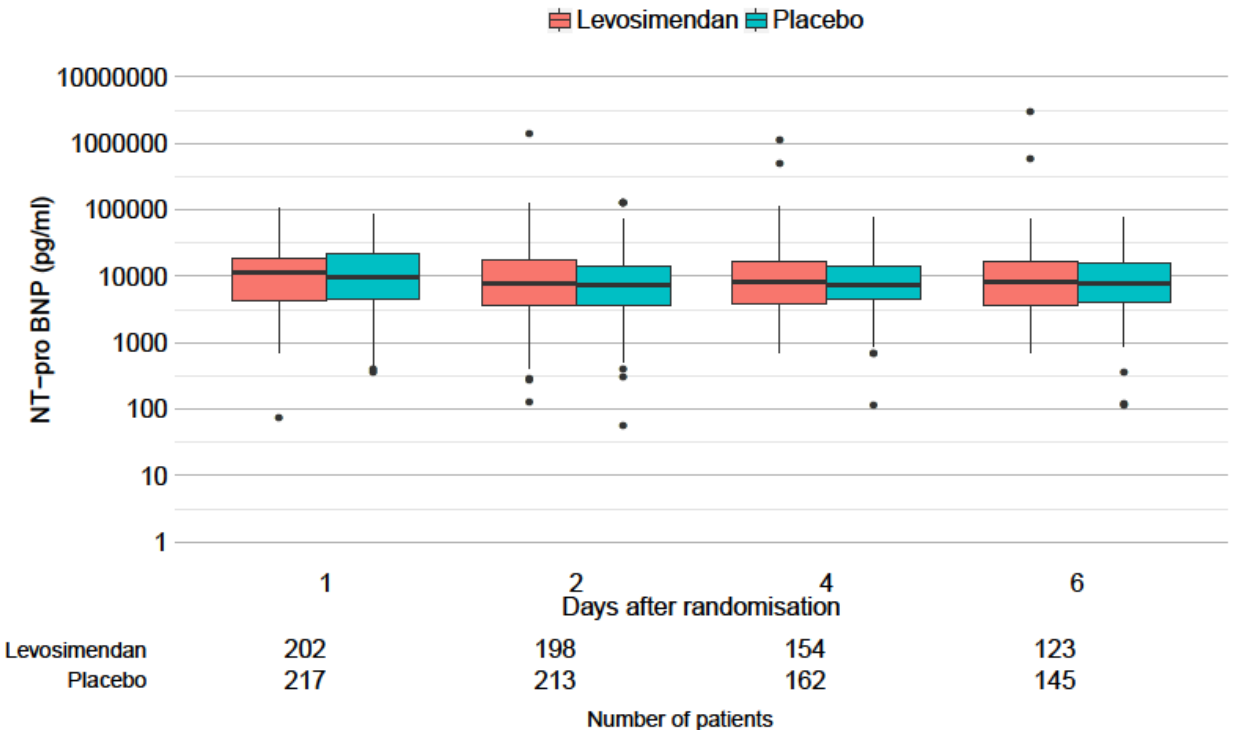


Figure S5: Boxplot of NT-pro BNP (pg/ml) by day and treatment

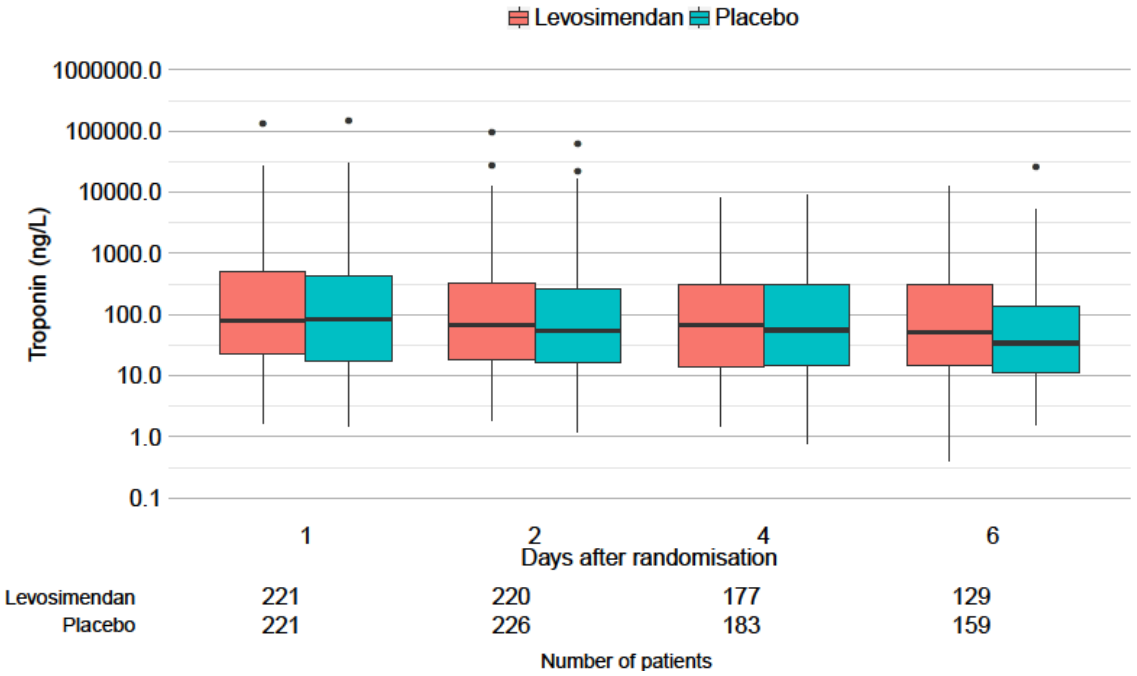


Figure S6: Boxplot of Troponin (ng/l) by day and treatment

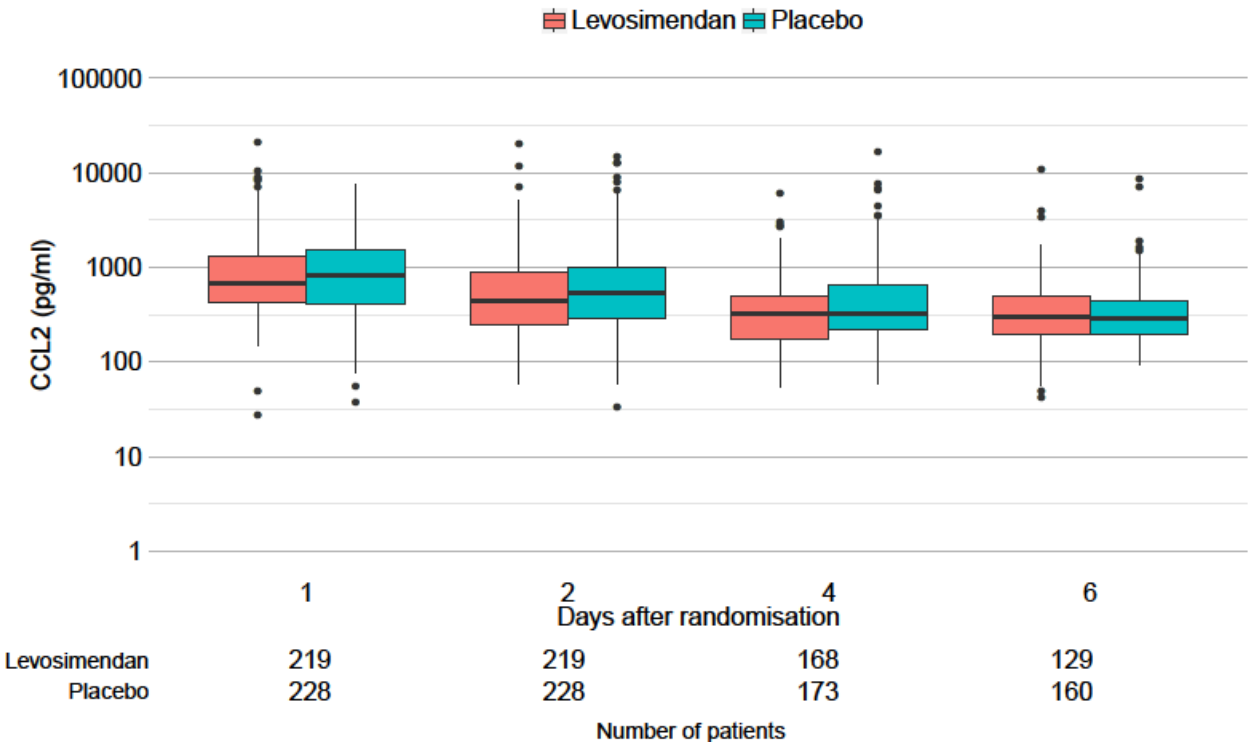


Figure S7: Boxplot of CCL2 (pg/ml) by day and treatment

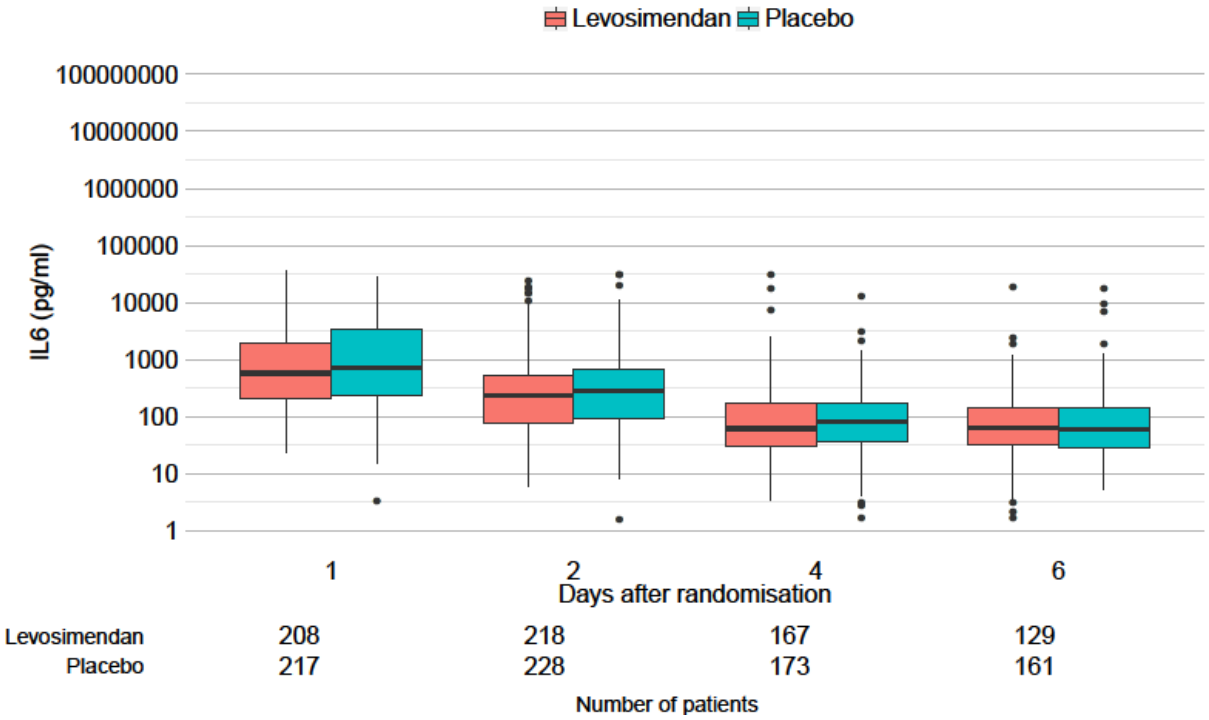


Figure S8: Boxplot of IL-6 (pg/ml) by day and treatment

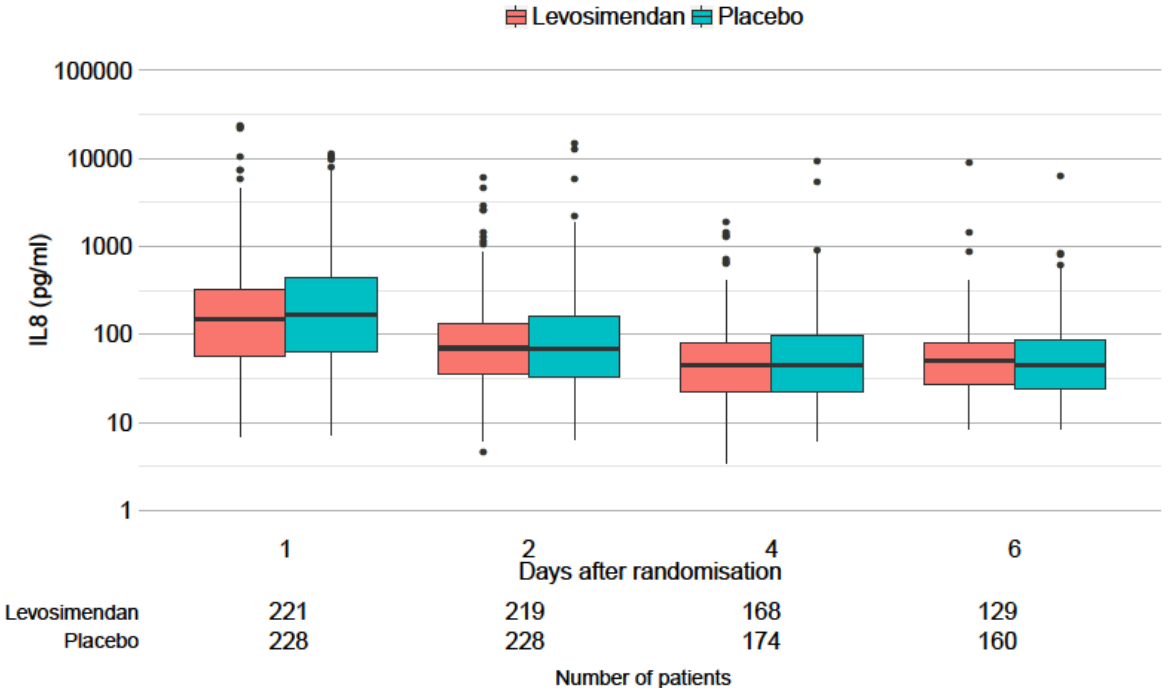


Figure S9: Boxplot of IL-8 (pg/ml) by day and treatment

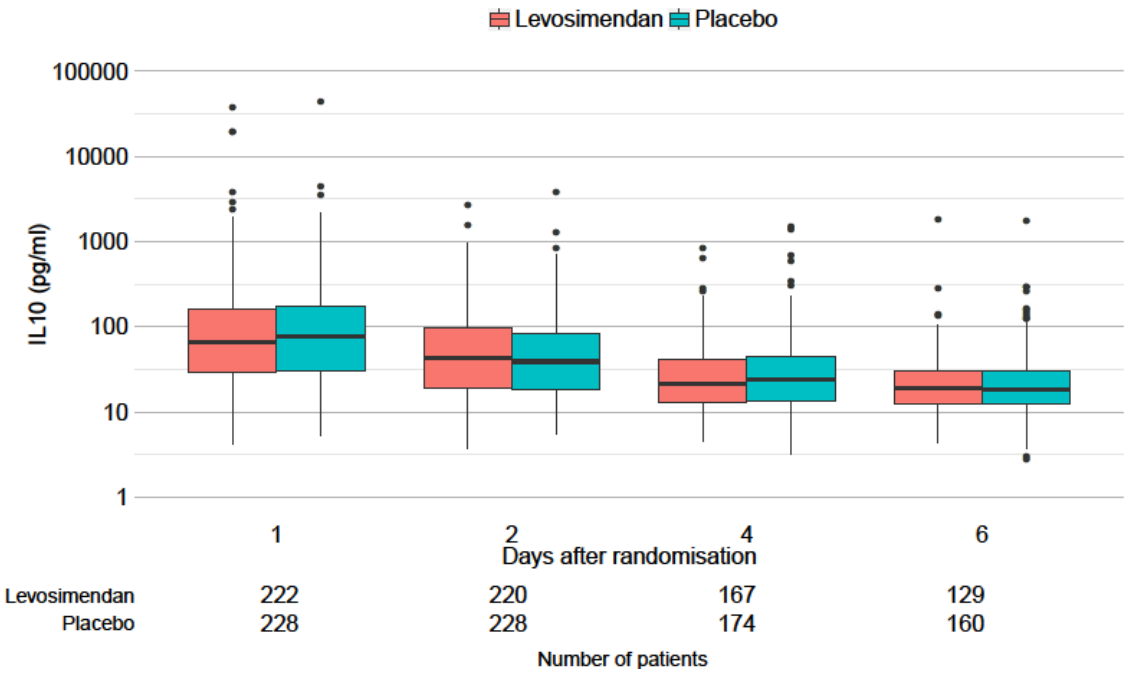


Figure S10: Boxplot of IL-10 (pg/ml) by day and treatment

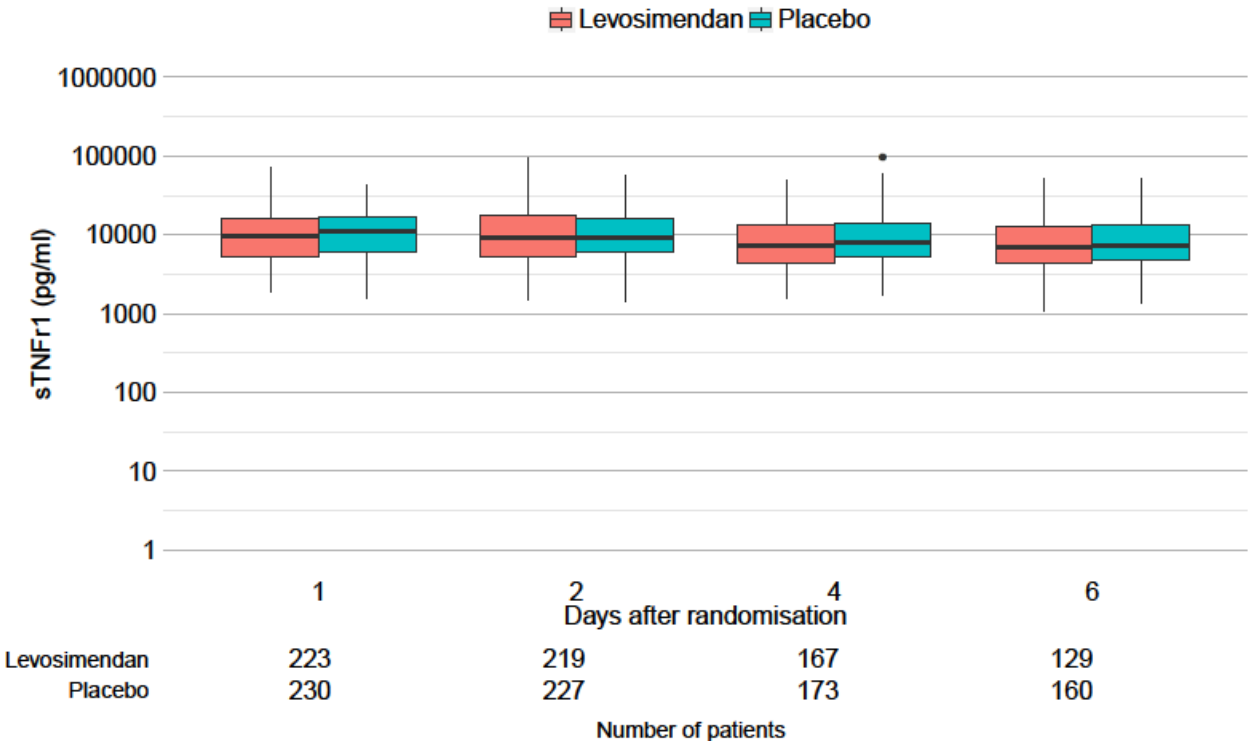


Figure S11: Boxplot of sTNFr1 (pg/ml) by day and treatment

Subgroup analysis of mean SOFA scores and 28 day mortality by cardiovascular markers

Table S25: Mean total SOFA score between randomisation and ICU discharge, normal baseline troponin

	Levosimendan		Placebo		Absolute difference (L-P)	
	mean (SD)	median (lq,uq)*	mean (SD)	median (lq,uq)*	mean (95% CI)†	median (95% CI)†
respiration	1.55 (1.1)	1.57 (0.67,2.57)	1.51 (1.06)	1.46 (0.67,2.17)	0.04(-0.30,0.39)	0.11(-0.58,0.71)
coagulation	0.55 (0.85)	0.11 (0,0.75)	0.51 (0.78)	0.11 (0,0.89)	0.04(-0.22,0.30)	0.00(-0.28,0.24)
liver	0.34 (0.66)	0 (0,0.24)	0.36 (0.66)	0 (0,0.41)	-0.01(-0.22,0.20)	0.00(0.00,0.00)
cardiovascular	1.94 (1.07)	1.71 (1.17,2.67)	1.85 (1.07)	1.59 (1,2.45)	0.09(-0.25,0.42)	0.12(-0.28,0.54)
renal	1.06 (1.33)	0.33 (0,1.86)	0.93 (1.23)	0.2 (0,1.69)	0.13(-0.27,0.53)	0.13(-0.49,0.80)
Total	5.44 (3.34)	4.67 (3.43,6)	5.16 (3.15)	4.29 (3.17,6)	0.28(-0.74,1.31)	0.38(-0.49,1.21)
√Total‡	2.23 (0.68)	2.16 (1.85,2.45)	2.18 (0.65)	2.07 (1.78,2.45)	0.05(-0.16,0.26)	0.09(-0.11,0.28)
Total no CVS	3.51 (2.64)	3 (2,4.14)	3.31 (2.41)	3 (1.73,3.98)	0.20(-0.59,1.00)	0.00(-0.66,0.57)

* lq=lower quartile, uq=upper quartile; † calculated using bootstrap; ‡Presented on the square root scale as there is no suitable back-transform to an interpretable scale

Table S26: Mean total SOFA score between randomisation and ICU discharge, raised baseline troponin

	Levosimendan		Placebo		Absolute difference (L-P)	
	mean (SD)	median (lq,uq)*	mean (SD)	median (lq,uq)*	mean (95% CI)†	median (95% CI) †
respiration	1.63 (1.15)	1.48 (0.74,2.63)	1.46 (1.08)	1.49 (0.47,2.2)	0.16(-0.09,0.42)	-0.01(-0.29,0.44)
coagulation	0.88 (1.14)	0.28 (0,1.42)	0.81 (1.07)	0.36 (0,1.1)	0.07(-0.18,0.33)	-0.08(-0.42,0.35)
liver	0.61 (0.92)	0 (0,1)	0.45 (0.79)	0 (0,0.58)	0.16(-0.03,0.36)	0.00(-0.09,0.20)
cardiovascular	2.23 (1.19)	2 (1.21,3.35)	1.88 (1.15)	1.54 (1,2.71)	0.34(0.07,0.61)	0.46(-0.03,0.85)
renal	1.52 (1.45)	1.2 (0.08,2.81)	1.3 (1.3)	0.96 (0.09,2.25)	0.22(-0.09,0.54)	0.24(-0.50,0.99)
Total	6.87 (4.04)	6.1 (3.77,9)	5.9 (3.73)	5.17 (3.3,7.77)	0.97(0.08,1.86)	0.93(-0.25,1.94)
√Total‡	2.51 (0.76)	2.47 (1.94,3)	2.31 (0.77)	2.27 (1.82,2.79)	0.20(0.03,0.38)	0.20(-0.05,0.41)
Total no CVS	4.64 (3.23)	4 (2.15,6.05)	4.02 (3.01)	3.52 (1.88,5.13)	0.63(-0.09,1.34)	0.48(-0.32,1.43)

* lq=lower quartile, uq=upper quartile; † calculated using bootstrap; ‡Presented on the square root scale as there is no suitable back-transform to an interpretable scale

Table S27: Mean total SOFA score between randomisation and ICU discharge, baseline troponin below median value

	Levosimendan		Placebo		Absolute difference (L-P)	
	mean (SD)	median (lq,uq)*	mean (SD)	median (lq,uq)*	mean (95% CI)†	median (95% CI) †
respiration	1.57 (1.05)	1.5 (0.85,2.55)	1.51 (1.01)	1.5 (0.67,2.14)	0.07(-0.21,0.34)	0.00(-0.38,0.57)
coagulation	0.63 (0.88)	0.18 (0,1)	0.6 (0.91)	0.15 (0,1)	0.03(-0.21,0.26)	0.04(-0.24,0.31)
liver	0.43 (0.77)	0 (0,0.5)	0.37 (0.69)	0 (0,0.43)	0.06(-0.13,0.26)	0.00(0.00,0.07)
cardiovascular	2.08 (1.1)	1.96 (1.18,3)	1.77 (1.05)	1.5 (1,2.36)	0.31(0.03,0.59)	0.46(0.07,0.74)
renal	1.15 (1.32)	0.53 (0,2)	0.98 (1.21)	0.4 (0,1.64)	0.17(-0.16,0.51)	0.14(-0.39,0.75)
Total	5.87 (3.38)	5 (3.67,7.27)	5.23 (3.16)	4.5 (3.05,6.05)	0.64(-0.22,1.50)	0.50(-0.20,1.44)
√Total‡	2.33 (0.68)	2.24 (1.91,2.7)	2.19 (0.67)	2.12 (1.74,2.46)	0.14(-0.04,0.32)	0.11(-0.05,0.33)
Total no CVS	3.79 (2.69)	3.14 (2,4.9)	3.46 (2.47)	3 (1.73,4.45)	0.33(-0.34,1.00)	0.14(-0.35,0.69)

* lq=lower quartile, uq=upper quartile; † calculated using bootstrap; ‡Presented on the square root scale as there is no suitable back-transform to an interpretable scale

Table S28: Mean total SOFA score between randomisation and ICU discharge, baseline troponin above median value

	Levosimendan		Placebo		Absolute difference (L-P)	
	mean (SD)	median (lq,uq)*	mean (SD)	median (lq,uq)*	mean (95% CI)†	median (95% CI)†
respiration	1.63 (1.22)	1.43 (0.56,2.79)	1.45 (1.13)	1.43 (0.33,2.27)	0.18(-0.13,0.49)	0.00(-0.38,0.60)
coagulation	0.9 (1.21)	0.16 (0,1.38)	0.81 (1.06)	0.36 (0,1.09)	0.09(-0.21,0.39)	-0.19(-0.58,0.39)
liver	0.61 (0.91)	0 (0,1)	0.46 (0.8)	0 (0,0.65)	0.14(-0.08,0.37)	0.00(-0.11,0.22)
cardiovascular	2.17 (1.21)	1.76 (1.11,3.34)	1.98 (1.18)	1.67 (1,3)	0.19(-0.12,0.51)	0.10(-0.36,0.64)
renal	1.58 (1.5)	1.2 (0.05,3)	1.37 (1.33)	1.06 (0.1,2.37)	0.21(-0.17,0.58)	0.14(-0.66,1.07)
Total	6.88 (4.25)	6.05 (3.73,9.15)	6.07 (3.88)	5.31 (3.33,8)	0.81(-0.25,1.88)	0.74(-0.77,1.79)
√Total‡	2.5 (0.8)	2.46 (1.93,3.02)	2.34 (0.78)	2.3 (1.83,2.83)	0.16(-0.05,0.37)	0.16(-0.16,0.37)
Total no CVS	4.71 (3.37)	4 (2.05,6.4)	4.09 (3.14)	3.77 (1.92,5.13)	0.62(-0.24,1.47)	0.23(-0.73,1.42)

* lq=lower quartile, uq=upper quartile; † calculated using bootstrap; ‡Presented on the square root scale as there is no suitable back-transform to an interpretable scale

Table S29: Mean total SOFA score between randomisation and ICU discharge, "normal" baseline NT-pro BNP

	Levosimendan		Placebo		Absolute difference (L-P)	
	mean (SD)	median (lq,uq)*	mean (SD)	median (lq,uq)*	mean (95% CI)†	median (95% CI) †
respiration	1.48 (1.04)	1.73 (0.67,2.15)	1.31 (1.11)	1.27 (0.26,1.9)	0.17(-0.45,0.77)	0.45(-0.80,1.29)
coagulation	0.47 (0.76)	0.06 (0,0.38)	0.29 (0.79)	0 (0,0)	0.18(-0.26,0.64)	0.06(0.00,0.38)
liver	0.11 (0.25)	0 (0,0)	0.41 (0.83)	0 (0,0.62)	-0.30(-0.65,-0.02)	0.00(-0.30,0.00)
cardiovascular	1.96 (1.06)	1.96 (1.21,2.5)	1.81 (1.24)	1.52 (0.86,2.71)	0.15(-0.50,0.81)	0.44(-0.63,1.24)
renal	0.57 (1.1)	0 (0,0.33)	1.08 (1.42)	0.17 (0,1.99)	-0.51(-1.21,0.22)	-0.17(-1.18,0.23)
Total	4.59 (1.71)	4.4 (3.67,5.46)	4.9 (3.57)	4.04 (2.68,6.62)	-0.31(-1.82,1.15)	0.36(-0.63,1.68)
√Total‡	2.11 (0.39)	2.1 (1.91,2.34)	2.05 (0.85)	2.01 (1.64,2.56)	0.06(-0.29,0.41)	0.09(-0.15,0.40)
Total no CVS	2.63 (1.14)	2.54 (2,3)	3.09 (2.8)	2.55 (0.76,4.12)	-0.46(-1.60,0.63)	-0.01(-1.14,1.13)

* lq=lower quartile, uq=upper quartile; † calculated using bootstrap; ‡Presented on the square root scale as there is no suitable back-transform to an interpretable scale

Table S30: Mean total SOFA score between randomisation and ICU discharge, raised baseline NT-pro BNP

	Levosimendan		Placebo		Absolute difference (L-P)	
	mean (SD)	median (lq,uq)*	mean (SD)	median (lq,uq)*	mean (95% CI)†	median (95% CI) †
respiration	1.57 (1.14)	1.41 (0.67,2.57)	1.49 (1.08)	1.46 (0.5,2.24)	0.08(-0.14,0.31)	-0.06(-0.32,0.39)
coagulation	0.81 (1.09)	0.21 (0,1.32)	0.77 (1)	0.38 (0,1.09)	0.04(-0.17,0.25)	-0.16(-0.42,0.18)
liver	0.59 (0.9)	0 (0,1)	0.42 (0.75)	0 (0,0.48)	0.16(0.00,0.33)	0.00(-0.01,0.17)
cardiovascular	2.19 (1.17)	1.86 (1.22,3.19)	1.9 (1.11)	1.59 (1,2.65)	0.29(0.06,0.52)	0.26(0.01,0.61)
renal	1.53 (1.44)	1.2 (0.1,2.83)	1.19 (1.29)	0.69 (0,2)	0.34(0.06,0.61)	0.51(-0.09,1.05)
Total	6.68 (4.03)	5.57 (3.8,8.56)	5.77 (3.63)	4.86 (3.2,7.12)	0.91(0.14,1.69)	0.71(-0.31,1.42)
√Total‡	2.47 (0.77)	2.36 (1.95,2.92)	2.29 (0.72)	2.2 (1.79,2.67)	0.18(0.03,0.33)	0.16(-0.07,0.31)
Total no CVS	4.5 (3.22)	3.71 (2.2,5.96)	3.87 (2.9)	3.33 (1.86,5)	0.62(0.00,1.24)	0.38(-0.27,0.96)

* lq=lower quartile, uq=upper quartile; † calculated using bootstrap; ‡Presented on the square root scale as there is no suitable back-transform to an interpretable scale

Table S31: Mean total SOFA score between randomisation and ICU discharge, baseline NT-pro BNP below median value

	Levosimendan		Placebo		Absolute difference (L-P)	
	mean (SD)	median (lq,uq)*	mean (SD)	median (lq,uq)*	mean (95% CI)†	median (95% CI) †
respiration	1.36 (0.99)	1.23 (0.64,2.06)	1.42 (1.07)	1.34 (0.5,2.15)	-0.05(-0.33,0.23)	-0.11(-0.45,0.31)
coagulation	0.57 (0.83)	0.13 (0,0.75)	0.59 (0.92)	0 (0,1)	-0.02(-0.26,0.22)	0.13(-0.12,0.35)
liver	0.38 (0.69)	0 (0,0.53)	0.38 (0.73)	0 (0,0.4)	0.00(-0.19,0.19)	0.00(0.00,0.03)
cardiovascular	1.94 (1.08)	1.65 (1.14,2.69)	1.85 (1.13)	1.54 (1,2.66)	0.09(-0.21,0.39)	0.11(-0.22,0.57)
renal	1.01 (1.18)	0.45 (0,1.69)	1.02 (1.26)	0.39 (0,1.7)	-0.02(-0.35,0.31)	0.05(-0.49,0.71)
Total	5.26 (2.87)	4.54 (3.35,6.35)	5.25 (3.35)	4.31 (3.1,6.54)	0.00(-0.84,0.84)	0.22(-0.48,0.92)
√Total‡	2.21 (0.61)	2.13 (1.83,2.52)	2.17 (0.73)	2.08 (1.76,2.56)	0.04(-0.14,0.22)	0.05(-0.11,0.22)
Total no CVS	3.32 (2.19)	2.94 (1.78,4.55)	3.41 (2.63)	2.92 (1.67,4.59)	-0.09(-0.74,0.56)	0.02(-0.67,0.55)

* lq=lower quartile, uq=upper quartile; † calculated using bootstrap; ‡Presented on the square root scale as there is no suitable back-transform to an interpretable scale

Table S32: Mean total SOFA score between randomisation and ICU discharge, baseline NT-pro BNP above median value

	Levosimendan		Placebo		Absolute difference (L-P)	
	mean (SD)	median (lq,uq)*	mean (SD)	median (lq,uq)*	mean (95% CI)†	median (95% CI)†
respiration	1.74 (1.22)	1.62 (0.69,2.91)	1.52 (1.09)	1.55 (0.52,2.27)	0.23(-0.08,0.54)	0.07(-0.32,0.89)
coagulation	0.98 (1.22)	0.3 (0,1.77)	0.83 (1.03)	0.43 (0,1.08)	0.15(-0.16,0.45)	-0.12(-0.61,0.55)
liver	0.7 (0.99)	0.08 (0,1.56)	0.47 (0.79)	0 (0,0.62)	0.23(-0.01,0.47)	0.08(-0.14,0.25)
cardiovascular	2.38 (1.19)	2.11 (1.38,3.8)	1.93 (1.12)	1.61 (1,2.61)	0.45(0.14,0.76)	0.50(0.09,1.05)
renal	1.85 (1.54)	1.9 (0.13,3.31)	1.35 (1.33)	1 (0.08,2.4)	0.50(0.12,0.89)	0.90(0.01,1.82)
Total	7.64 (4.41)	6.59 (4.29,10.92)	6.09 (3.88)	5.43 (3.27,7.65)	1.55(0.43,2.68)	1.15(0.16,2.37)
√Total‡	2.65 (0.8)	2.57 (2.07,3.3)	2.35 (0.75)	2.33 (1.81,2.77)	0.30(0.08,0.51)	0.24(0.03,0.48)
Total no CVS	5.26 (3.56)	4.43 (2.58,7.57)	4.16 (3.12)	3.83 (1.86,5.21)	1.10(0.20,2.01)	0.59(-0.41,1.83)

* lq=lower quartile, uq=upper quartile; † calculated using bootstrap; ‡Presented on the square root scale as there is no suitable back-transform to an interpretable scale

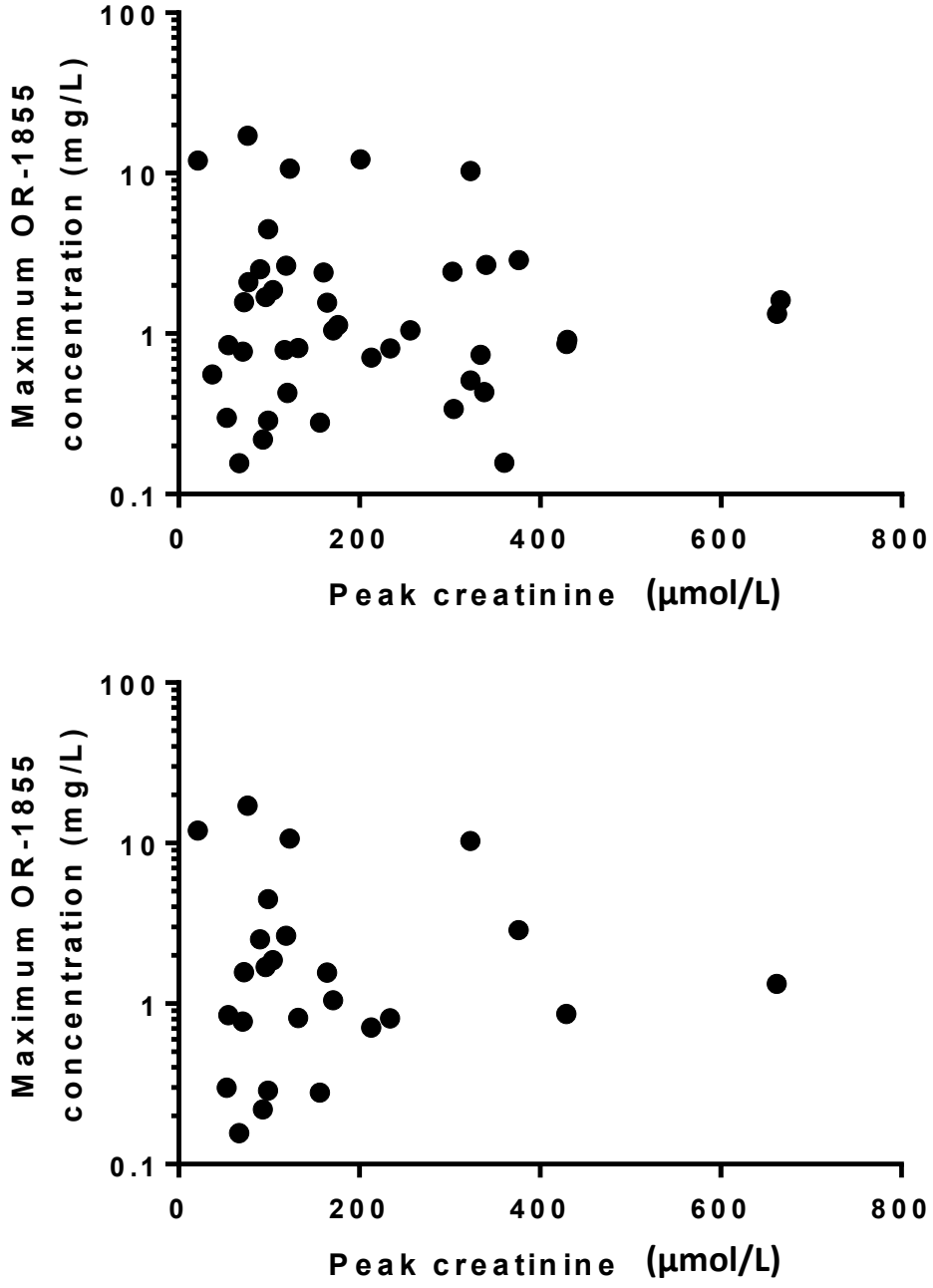


Figure S12: Impact of renal function on maximum OR-1855 concentration for all patients (top panel) and patients never receiving renal replacement therapy (bottom panel).

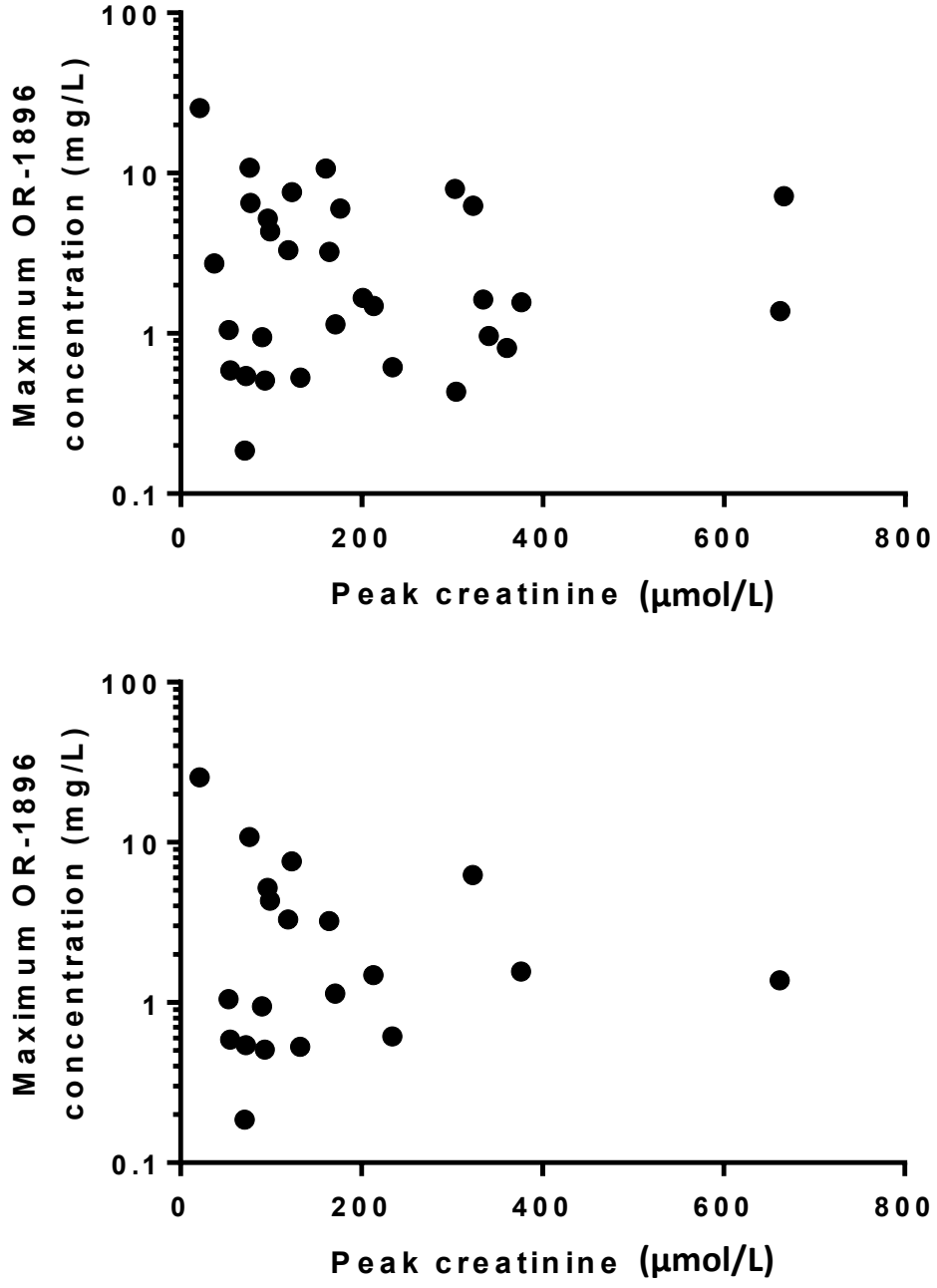


Figure S13: Impact of renal function on maximum OR-1896 concentration for all patients (top panel) and patients never receiving renal replacement therapy (bottom panel).

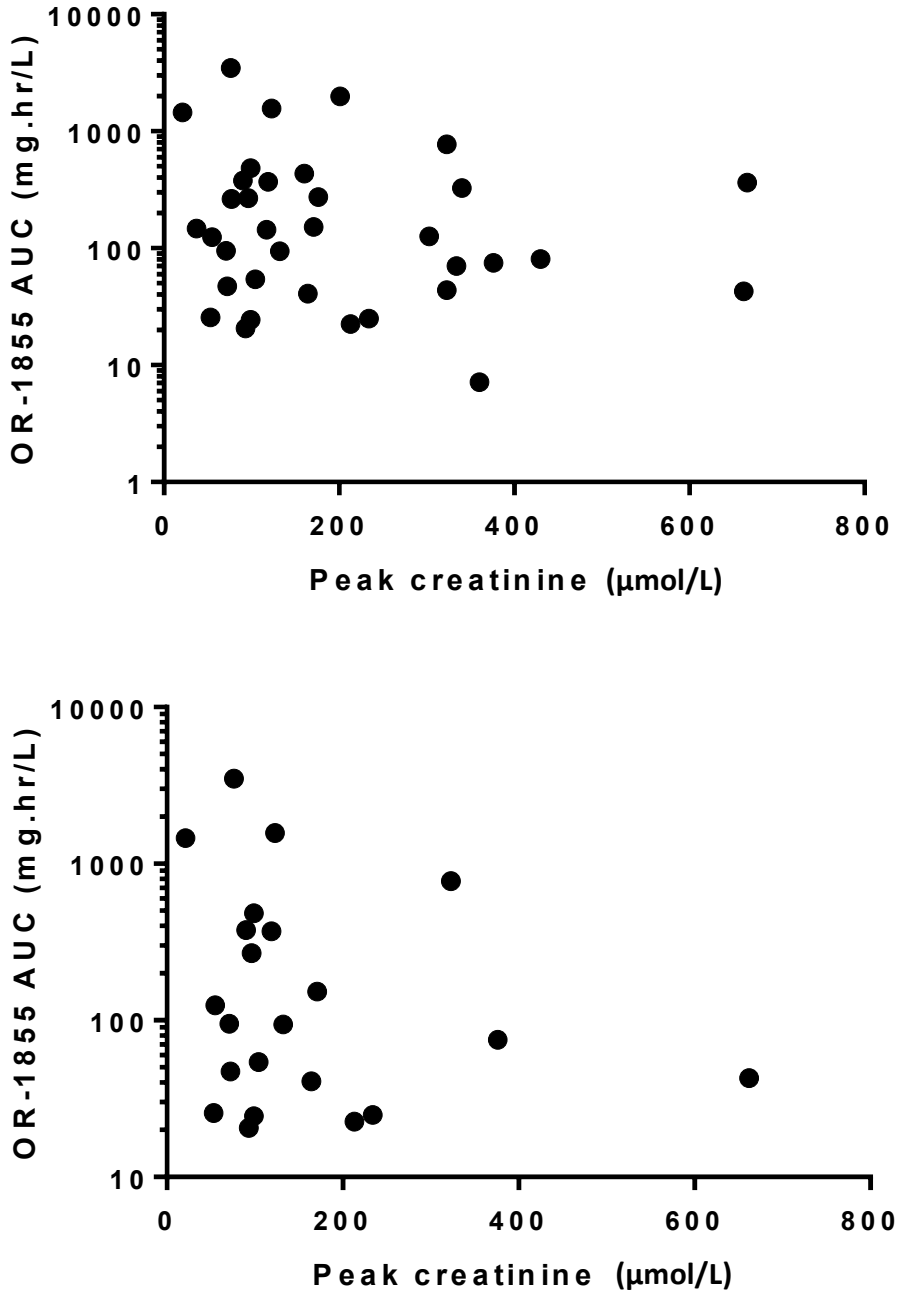


Figure S14: Impact of renal function on OR-1855 AUC for all patients (top panel) and patients never receiving renal replacement therapy (bottom panel).

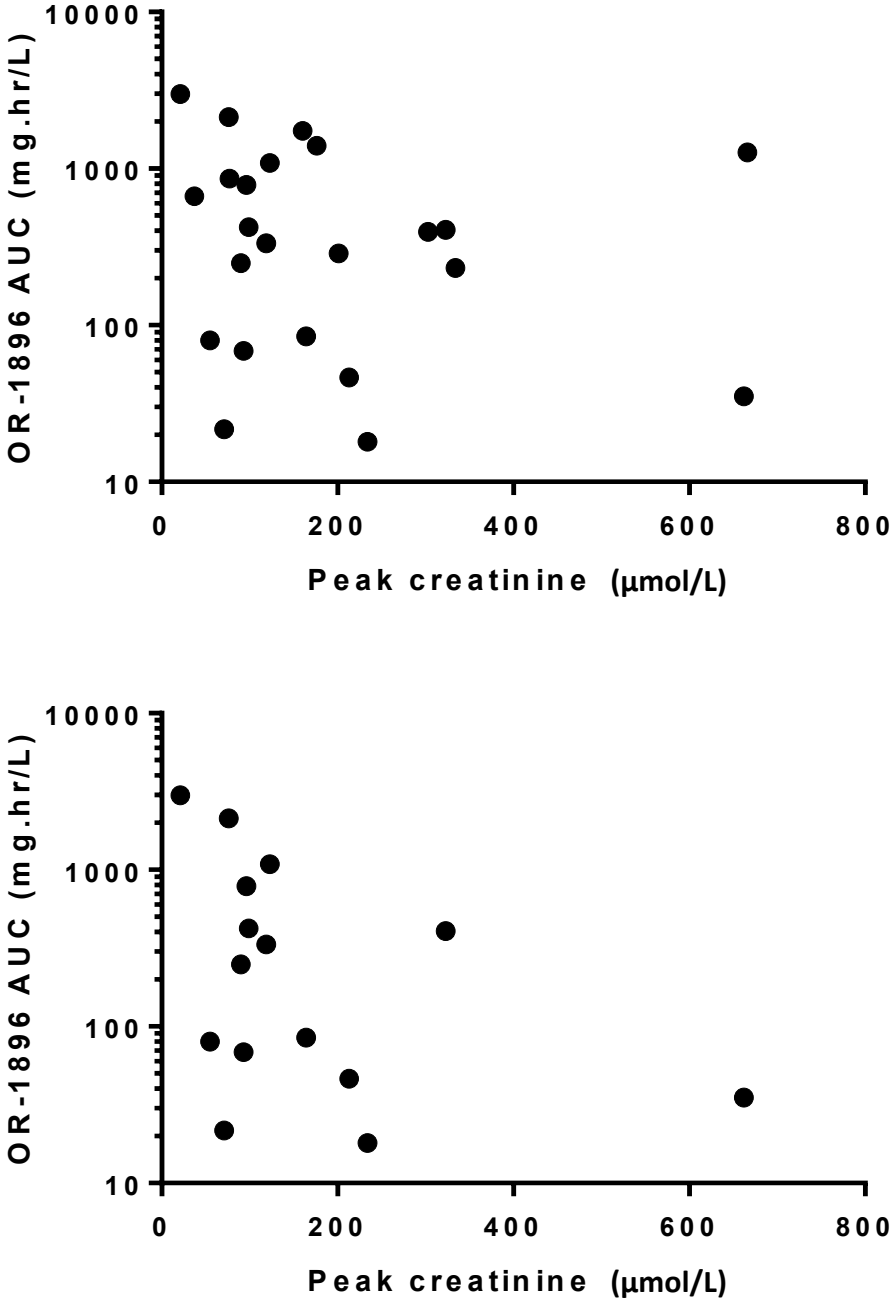


Figure S15: Impact of renal function on OR-1896 AUC for all patients (top panel) and patients never receiving renal replacement therapy (bottom panel).

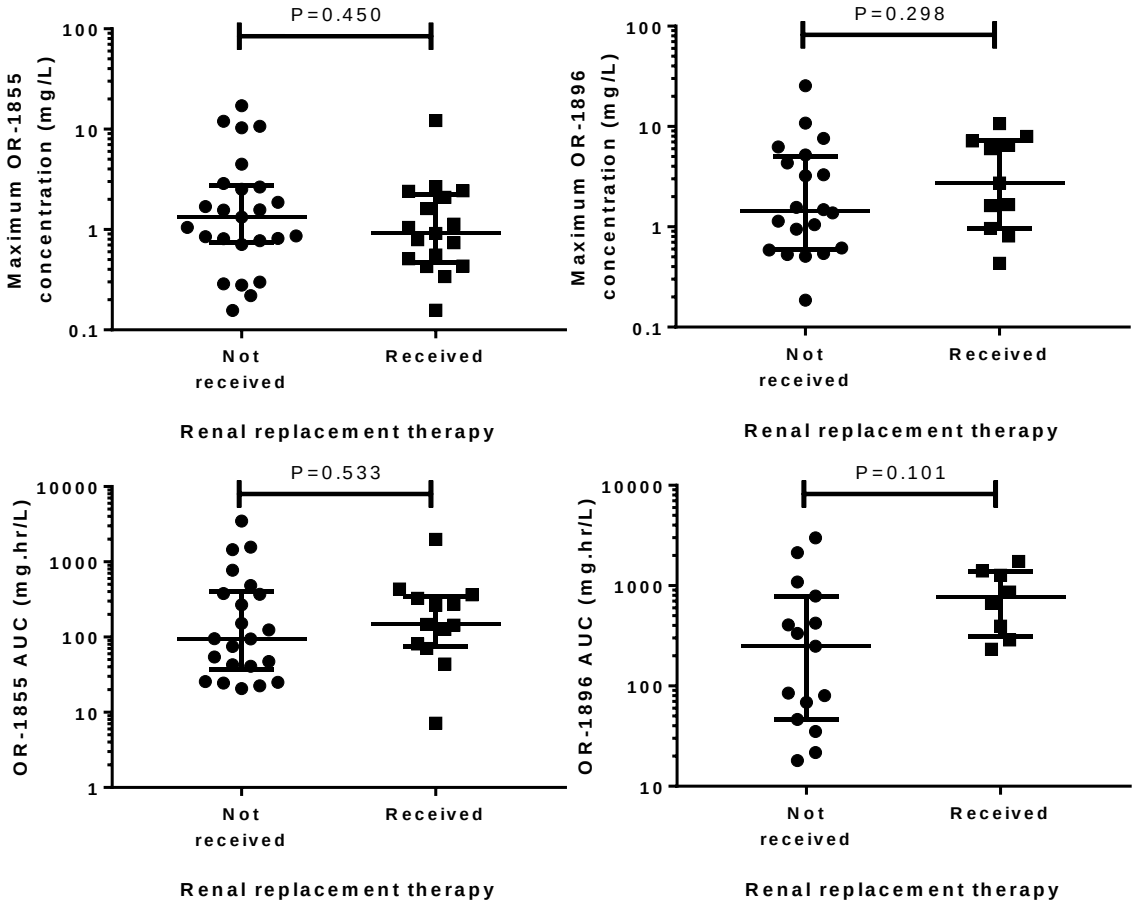


Figure S16: Effect of renal replacement therapy on maximum OR-1855 concentration (left, top) maximum OR-1896 concentrations (right, top), OR-1855 AUC (left, bottom) and OR-1896 AUC (right, bottom).

(Significance calculated by Mann-Whitney test; Median and inter-quartile ranges shown).

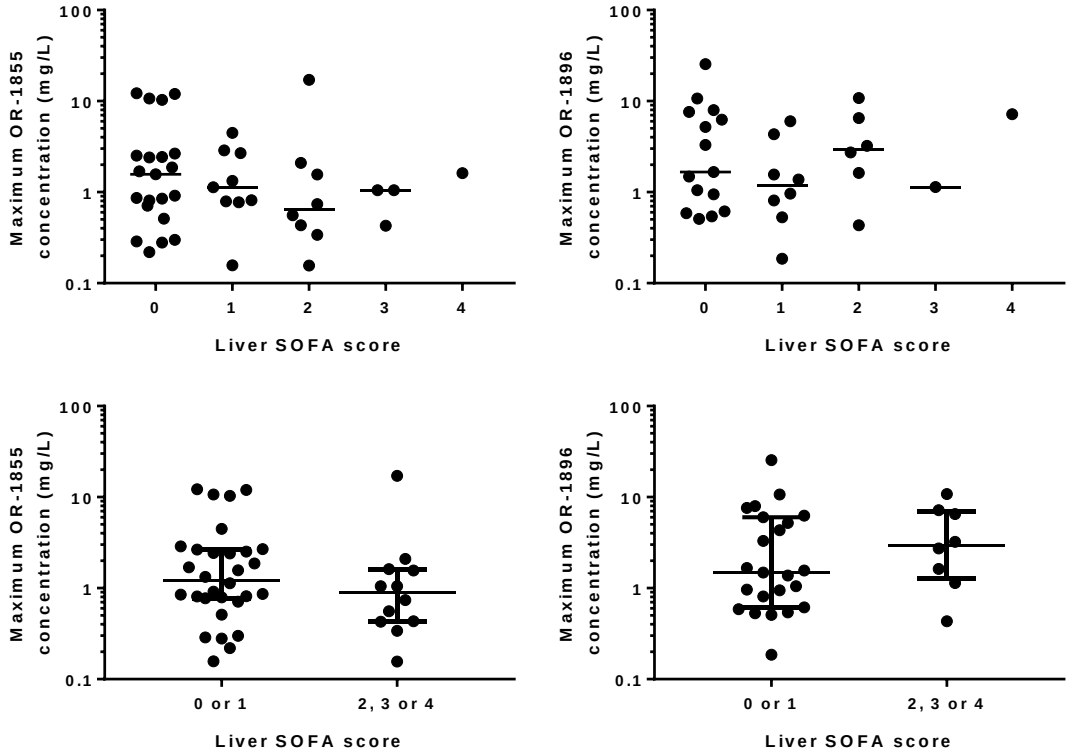


Figure S17: Impact of liver function on maximum OR-1855 (left panels) and OR-1896 (right panels) concentration.

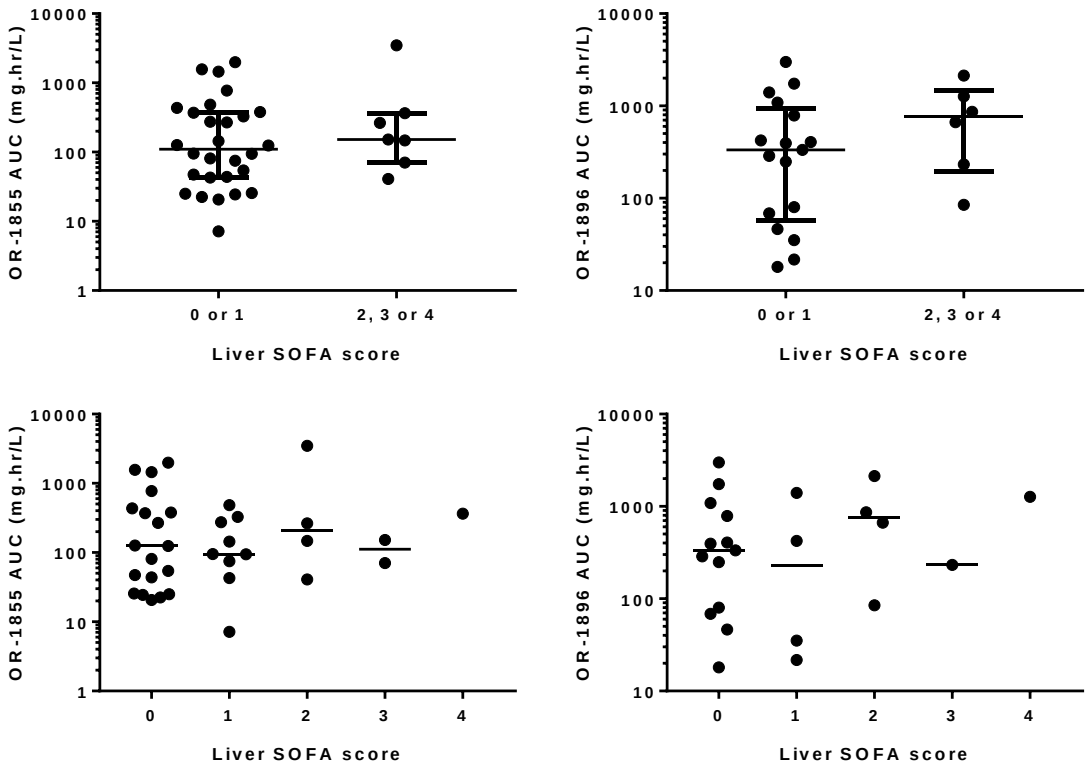


Figure S18: Impact of liver function on OR-1855 AUC (left panels) and OR-1896 AUC (right panels).

INFORM CLINICAL DATABASE

The data that are stored in InForm are summarised in this Appendix (taken from the LeoPARDS annotated study book, Version 1.0).

Inclusion & Exclusion

Inclusion criteria

• Patient has septic shock (yes/no)

• Age ≥ 18 (yes/no)

• Known or suspected infection (yes/no)

• Has required vasopressor support for > 4 hours and still has an ongoing vasopressor requirement(yes/no)

Two of the following four criteria are also required for inclusion into this study.

• Within last 24 hours: fever (> 380C) or hypothermia (< 360C) (yes/no)

• Within last 24 hours: tachycardia (heart rate > 90 beats per minute) (yes/no)

•Within last 24 hours: tachypnoea (respiratory rate > 20 breaths per minute or PaCO2 < 4.3 kPa) or need for mechanical ventilation (yes/no)

• Within last 24 hours: abnormal leukocyte count (> 12, 000 cells/mm3, < 4, 000 cells/mm3, or > 10% immature band forms) (yes/no)

Exclusion criteria

• More than 24 hours since meeting all the inclusion criteria (yes/no)

• End-stage renal failure at presentation (yes/no)

• Severe hepatic impairment (Child-Pugh class C) (yes/no)

• A history of Torsades de Pointes (yes/no)

• Known significant mechanical obstructions affecting ventricular filling or outflow or both (yes/no)

• Treatment limitation decision in place (yes/no)

• Known or estimated weight > 135kg (yes/no)

• Known to be pregnant (yes/no)

• Previous treatment with levosimendan within 30 days (yes/no)

• Known hypersensitivity to levosimendan or any of the excipients (yes/no)

•Known to have received another IMP within 30 days or currently in another interventional trial that might interact with the study drug or previously enrolled into LeoPARDS (yes/no)

Randomisation

•Has informed consent been obtained? (Patient - date the consent was signed/PerLR - date the consent was signed/ProLR - date the consent was signed/No)

• Do you want to randomise the patient? (yes/no)

• Name of person performing randomisation

• Study Drug ID

• Date and time of randomisation

• Unblinded Drug Details

• Did automated randomisation complete successfully? (yes/no/NA)

Manual Randomisation

•Was Study Drug ID allocated? (yes/no - Enter Manual Randomisation Study Drug Number and Date and time of randomisation)

• Unblinded drug code

Baseline evaluation

Event Dates

• Date of Hospital Admission

• Date and time of ICU admission

•Type and Reason for ICU admission (Medical + coded list/Surgery - Emergency + coded list/Surgery - Elective + coded list)

• Date and time of starting a continuous vasopressor infusion

• Date and time of starting the study drug

•Source of infection (Lung/Abdomen/Urine/Primary bacteraemia/Neurological/Soft tissue or line/Other - specify)

• Causative organism known? (Yes/No: if Yes, Bacteria + coded list/Fungi + coded list/Parasite
+ coded list/Virus + coded list/Mixed, specify)

• Any additional comments?

Comorbidites

• Ischaemic heart disease (yes/no)

• NYHA Class IV (yes/no)

• Cardiac failure requiring medical treatment (yes/no)

• Does the patient normally take beta-blockers for any indication (yes/no)

• Severe COPD (yes/no)

• Chronic renal failure (yes/no)

• Normal baseline creatinine (for all patients) (µmol/l)

• Cirrhosis (yes/no)

• Immunocompromised (yes/no)

• Diabetes (yes/no)

Apache 2

The APACHE II score will be calculated over the 24 hour period prior to inclusion in the study. Accordingly, the values recorded on this form are based on all available measurements in the 24 hours preceding inclusion (for some patients this may be a shorter time period). The following data are used to calculate the acute physiologic score (APS points):

• Temperature (C): Highest and Lowest

• Mean Arterial Pressure (mmHg): Highest and Lowest

• Heart Rate (beats/min): Highest and Lowest

• Respiratory Rate (resp/min): Highest and Lowest

• Lowest PaO2 (kPa), FiO2 with lowest PaO2, PaCO2 with lowest PaO2 (kPa)

• Highest FiO2, PaO2 with highest FiO2 (kPa), PaCO2 with highest FiO2 (kPa)

• pH: Highest and Lowest

• Na (mmol/l): Highest and Lowest

• K (mmol/l): Highest and Lowest

• Creatinine (µmol/l): Highest and Lowest

• Acute Renal Failure (yes/no)

• Hb (g/l): Highest and Lowest

• WBC (×109/l): Highest and Lowest

• Lowest GCS off sedation

The age score (AGE points) are calculated using:

• Date of birth

In addition chronic health points are calculated using data from the Event Dates and Comorbidites forms. The Total APACHE II score is then automatically calculated by adding the APS points, AGE points and chronic health points.

This form also includes the question, “Are any values missing? (yes/no)”.

Demographics

• Date of birth

• Age

• Sex (male/female)

• Ethnicity (Caucasian/Black/Asian/Other, specify)

• Height (cm)

• Weight (kg)

Baseline Physiology

For this form, the last values collected before initiating study drug infusion are entered (for con- tinuously monitored measurements, this is likely to be within the last hour).

• Mean arterial pressure (mmHg)

• Heart rate (beats/min)

• Heart Rhythm (Sinus Rhythm/Atrial Fibrillation/Paced/Other irregular rhythm)

• Central venous pressure (mmHg)

• SaO2 (%)

• ScvO2 (%)

• Was Cardiac output measured? (yes, Cardiac output in L/min /no)

• Lactate (mmol/l)

•Vasoactive drugs (Noradrenaline (Dose in µg/kg/min), Adrenaline (Dose in µg/kg/min), Va- sopressin (Dose in Units/min), Terlipressin (Dose in µg/kg/hr or mg/6hr), Dobutamine (Dose in µg/kg/min), GTN (Dose in mg/hr) and Other (drug name, unit and dose))

• IV fluid volume in last 4 hours (mls)

• PaO2 (kPa)

• FiO2

• Mechanical ventilation (yes/no)

•Does the patient have moderate or severe ARDS? (PaO_2/FiO_2 < 26.7kPa, PEEP≥ 5cm H2O & bilat opacities on CXR) (yes/no)

• Creatinine (µmol/l)

• Renal replacement therapy (yes/no)

• Bilirubin (µmol/l)

• Hb (g/l)

• Platelets (×103/mm3)

• GCS

Daily evaluation

6 Hours

• Dose of study drug (mls/hr)

• MAP - mean arterial pressure (mmHg)

• CVP - central venous pressure (mmHg)

• HR - heart rate (beats/min)

• Heart Rhythm (Sinus Rhythm/Atrial Fibrillation/Paced/Other irregular rhythm)

• ScvO2 (%)

• Was cardiac output measured? (yes, Cardiac output in L/min /no)

• Lactate (mmol/l)

• SaO2 (%)

• Hb (g/l)

• Total IV fluid in last 6 hours (mls)

• Fluid balance (all input and output) in last 6 hours (mls)

•Vasoactive drugs (None / Noradrenaline (Dose in µg/kg/min), Adrenaline (Dose in µg/kg/min), Vasopressin (Dose in Units/min), Terlipressin (Dose in µg/kg/hr or mg/6hr), Dobutamine (Dose in µg/kg/min), GTN (Dose in mg/hr) and Other (drug name, unit and dose))

12 Hours

As for 6 Hours.

24 Hours

As for 6 Hours, apart from Total IV fluid and Fluid balance which change to:

• Total IV fluid in last 12 hours (mls)

• Fluid balance (all input and output) in last 12 hours (mls)

Daily Data

• Mechanical ventilation (yes/no)

• Lowest PaO2/FiO2 ratio (Lowest PaO2/FiO2 ratio (whilst ventilated if ventilated today) (kPa)

/ Not Done)

• Highest Creatinine (µmol/l)

• Did the patient receive any beta-blockers today (yes/no)

•Total urine output in 24 hours (if less than 24 hours, please enter measured volume and number of hours in the box) (mls)

• No of hours (if less than 24 hours urine output recorded on admission)

• Urine output 0mls for 12 hours+ (yes/no)

• Urine output < 0.5ml/kg/hr for 12 hours+ (yes/no)

• Urine output < 0.5ml/kg/hr for 6 hours+ (yes/no)

• Renal replacement therapy (yes/no)

• Highest Bilirubin (µmol/l)

• Lowest platelet count (×103/mm3)

• Did patient remain in ICU? (yes/no)

36 HR, 48 HR, 60 HR, 72 HR, 84 HR and 96 HR

As for 24 Hours, but without dose of study drug question.

Day 5+

• Lowest MAP (mmHg)

• Did the patient receive any beta-blockers today (yes/no)

•Vasoactive drugs (None / Noradrenaline (Dose in µg/kg/min), Adrenaline (Dose in µg/kg/min), Vasopressin (Dose in Units/min), Terlipressin (Dose in µg/kg/hr or mg/6hr), Dobutamine (Dose in µg/kg/min), GTN (Dose in µg/kg/hr) and Other (drug name, unit and dose))

• Mechanical ventilation (yes/no)

• Lowest PaO2/FiO2 ratio (Lowest PaO2/FiO2 ratio (whilst ventilated if ventilated today) (kPa)/ Not Done)

• Highest Creatinine (µmol/l)

• Total urine output in 24 hours (if less than 24 hours, please enter measured volume and number of hours in the box) (mls)

• Urine output 0mls for 12 hours+ (yes/no)

• Urine output < 0.5ml/kg/hr for 12 hours+ (yes/no)

• Urine output < 0.5ml/kg/hr for 6 hours+ (yes/no)

• Renal replacement therapy (yes/no)

• Highest Bilirubin (µmol/l)

• Lowest platelet count (×103/mm3)

• Did patient remain in ICU? (yes/no)

This is the same information as form Daily Data, plus Lowest MAP and details of vasoactive drugs, and minus the question on number of hours of urine collection.

Safety data

Adverse Event (AE)

• AE Number

• Adverse Event Description

• Onset Date

• Ongoing? (yes/no, end date)

• Severity (Mild/Moderate/Severe)

• Relationship to study medication (Not related/Unlikely/Possible/Probable/Definite/Not assessable)

• If at least possibly related to study drug, was it ‘expected’ (according to SmPC / protocol) or‘Unexpected’ (Expected/Unexpected)

• Action taken concerning study medication (None/Medication/Dose reduction/Temporarily dis- continued/Permanently discontinued)

• Outcome (Recovered/Not yet recovered/Death/Unknown)

• SAE Classification (Not serious/Serious, Death/Life threatening/Persistently disabling/Hospitalisation required/Congenital abnormality/Other medical important event - detail requested)

• Comments

SAE Report Form

• AE Number

• Type of report (Initial/Initial and final/Interim/Final)

• Why was the event serious? (Resulted in death/Life threatening/Resulted in congenital anomaly or birth defect/Resulted in persistent or significant disability or incapacity/Required inpatient hospitalisation or prolongation of existing/Other medically important event - detail requested)

• Briefly describe SAE

• Date of onset

• Severity (1=Mild/2=Moderate/3=Severe/4=Life threatening/5=Fatal)

• Outcome (Resolved/Resolved with sequelae/Persisting/Worsened/Fatal/Not assessable)

• Date of outcome

•Causal Relationship to event (Definitely/Probably/Possibly/Unlikely/Not related/Not assess- able)

• If at least possibly related to study drug, was it ‘expected’ (according to SmPC / protocol) or ‘Unexpected’ (Expected/Unexpected)

• Action taken (0=None/1=Dose reduction/2=Treatment delayed/3=Treatment delayed and re- duced/4=Permanently stopped)

• Was this event expected in view of the patient’s clinical history? (yes/no)

• Other relevant treatments at the time of the event Entry

• Treatment - Generic name of drug treatment given in the last 30 days

• Total Daily Dose and units

• Route of administration (Oral/Intravenous/Subcutaneous/Other - specify)

• Start Date

CI review

• SAE Number

• Was the SAE related to IMP? (Not related/Unlikely/Possible/Probable/Definite/Not assessable)

• Was the SAE expected? (yes/no/NA)

• Comments

Other

Outcomes

• Successfully weaned from mechanical ventilation for 48hours+? (yes, date and time of 1st successful weaning/Never mechanically ventilated/Died without ever weaning)

• Did the patient fulfil moderate or severe ARDS criteria at anytime after randomisation? (PaO_2/FiO_2 <26.7kPa, PEEP≥ 5cm H2O & bilat opacities on CXR) (yes/no)

• Status on ICU discharge (alive/dead)

• Date of ICU discharge

• Status on hospital discharge (alive/dead)

• Date of hospital discharge

• Status at start of day 29 (alive/dead)

• Did patient require renal replacement therapy after ICU discharge (yes, Date of last RRT session/no)

• Any additional comments?

CCMDS DATA

Information on resource usage is collected for the patient's whole ICU stay (beyond day 28 if they have not been discharged by then).

• Number of advanced respiratory support days (days)

• Number of basic respiratory support days (days)

• Number of advanced cardiovascular support days (days)

• Number of basic cardiovascular support days (days)
• Number of renal support days (days)
• Number of neurological support days (days)
• Number of gastrointestinal support days (days)
• Number of dermatological support days (days)
• Number of liver support days (days)

Samples

• Baseline sample collected? (yes: Date and time of sample, Sample type (Buffy Coat/Pax Gene/Plasma/Serum/Urine), Sample ID/no)
• 24-36hr sample collected? (yes: Date and time of sample, Sample type (Buffy Coat/Pax Gene/Plasma/Serum/Urine), Sample ID/no)
• Day 4 sample collected? (yes: Date and time of sample, Sample type (Buffy Coat/Pax Gene/Plasma/Serum/Urine), Sample ID/no)
• Day 6 sample collected? (yes: Date and time of sample, Sample type (Buffy Coat/Pax Gene/Plasma/Serum/Urine), Sample ID/no)

PK samples

• Any samples collected (yes/no)

For each sample, the following information is collected:

• Timepoint (23 - 24 hours/66 - 78 hours/Day 6/Day 8/Day 10/Day 13/Day 16)
• Date and time of sample
• Sample ID

Protocol Deviations (PD)

• Protocol Deviation number
• Date of Deviation
• Type of Protocol Deviation (Inclusion-exclusion criteria/Study drug administration/Study crossover/Sampling/Consent issue/Other, specify)
• Serious? (yes/no)
• Details of deviation
• Steps taken to rectify

• Trial Co-ordinator Comments

• Principal Investigator Comments

Study Completion/Termination

• Completion status (Completed/Incomplete, Termination date and Termination Reason (Patient withdrew/PerLR withdrew consent/Investigator decision/Termination of study/Termination other reason - specify))

• If consent is withdrawn, do they agree to data and samples already collected to be used for analysis? Data (yes/no); Sample (yes/no)

STATISTICAL DETAILS

Bayesian sensitivity analysis

As discussed in section 3.10.1 the overall level of missingness across SOFA components was 6.2%, higher than the 4% expected. Last observation carried forward methods may underestimate uncertainty so, as specified in the SAP, to check the robustness of the primary result a sensitivity analysis was conducted, implementing Bayesian models using Markov Chain Monte Carlo (MCMC) methods to impute missing values at a component level, based on a selection model factorisation. The underlying measurements were imputed rather than the SOFA scores to avoid loss of information. An autoregressive process was used to account for the longitudinal structure, with a vague prior on the autoregressive parameter describing the correlation of successive measurements. We applied a bootstrap approach to calculate the difference between treatment groups because of the non-normal distribution of the daily total SOFA scores, with a separate bootstrap sample taken at each MCMC iteration. The following informative prior distributions were specified for delta, the parameter describing the association between the SOFA score value and the log odds of the value being missing:

1. $\delta \sim N(0, 0.68)\ I(0,)$, a truncated Normal distribution restricted to positive values of δ, so that normal SOFA scores are more likely to be missing, with the association limited to a 5-fold change (presented in the main report)
2. $\delta = 0.69$, a point prior corresponding to a belief that normal SOFA scores are twice as likely to be missing, a stronger version of the assumption
3. $\delta = -0.69$, a point prior corresponding to a belief that normal SOFA scores are half as likely to be missing, a contradicting assumption

The SOFA scores were calculated using the imputed values and the mean total SOFA score compared between treatment arms. The full model code is provided at the end of this appendix. As with other Bayesian analyses, models were run in WinBUGS version 1.4. We used two chains with diffuse starting values and checked convergence using trace plots and the Gelman-Rubin convergence statistic. After convergence, MCMC simulations were run until the effective sample size was around 10,000.

Results obtained using point priors for δ (models 2 and 3) are shown in tables S33 and S34 below.

Table S33: Mean total SOFA score between randomisation and ICU discharge, intention to treat

Bayesian analysis with prior assumption that normal SOFA scores are twice as likely to be missing

	mean (SD)	mean (SD)	mean (95% CrI)†
respiration	1.93 (1.21)	1.82 (1.17)	0.12 (-0.09,0.32)
coagulation	0.83 (1.08)	0.86 (1.09)	-0.03 (-0.22,0.16)
liver	0.49 (0.82)	0.48 (0.81)	0.01 (-0.13,0.15)
cardiovascular	2.42 (1.13)	2.22 (1.15)	0.20 (0.00,0.40)
renal	1.57 (1.54)	1.43 (1.44)	0.14 (-0.12,0.40)
Total	7.24 (3.72)	6.81 (3.73)	0.43 (-0.22,1.09)

* lq=lower quartile, uq=upper quartile; †credible interval calculated using bootstrap

Table S34: Mean total SOFA score between randomisation and ICU discharge, intention to treat

Bayesian analysis with prior assumption that normal SOFA scores are half as likely to be missing

	mean (SD)	mean (SD)	mean (95% CrI)†
respiration	1.93 (1.21)	1.82 (1.17)	0.12 (-0.09,0.32)
coagulation	0.86 (1.09)	0.89 (1.09)	-0.03 (-0.22,0.17)
liver	0.49 (0.82)	0.48 (0.81)	0.01 (-0.13,0.15)
cardiovascular	2.42 (1.13)	2.22 (1.15)	0.20 (0.00,0.39)
renal	1.57 (1.54)	1.43 (1.44)	0.14 (-0.12,0.40)
Total	7.27 (3.72)	6.84 (3.73)	0.44 (-0.21,1.08)

* lq=lower quartile, uq=upper quartile; †credible interval calculated using bootstrap

Additional results for PaO_2/FiO_2 ratio and bilirubin analysis

PaO_2/FiO_2 ratio and bilirubin were analysed using a joint longitudinal and survival models (see sections 4.5.4.3 and 4.5.4.4 for PaO_2/FiO_2 ratio and bilirubin respectively). Table S35 and table S36 show the results for alternate specifications of the joint parameters, in comparison with the full model specified in the SAP, for PaO_2/FiO_2 ratio and bilirubin respectively.

Additional results for biomarker analysis

Table S37 to S43 show the full results from the hierarchical regression models for cardiovascular and inflammatory markers. The main results included only the parameters relating to the treatment effect. Here all results are included, along with those for sensitivity analysis adjusting for age and APACHE II score, and for ICU effects. The Deviance Information Criterion (DIC) is included as a measure of model fit. The model with the smallest DIC is considered to fit the data best, though alternative models with a difference of less than 3 should not be ruled out, and differences of less than 7 indicate weak support for the “best” model.

Table S35: Estimated effects of levosimendan on PaO_2/FiO_2 ratio from joint longitudinal and survival models;

Alternative specifications for joint parameters

	Full model	Separate models	γ_1 only	γ_1 and γ_2 only
Change per day - Levosimendan (kPa)	1.23 (0.95,1.53)	0.59 (0.30,0.88)	0.59 (0.29,0.88)	0.32 (0.06,0.59)
Change per day - Placebo (kPa)	0.77 (0.50,1.05)	0.17 (-0.12,0.45)	0.17 (-0.12,0.47)	0.19 (-0.07,0.46)
Pr(faster improvement in Levosimendan)	0.996	0.978	0.972	0.743
Treament difference on day 1 (kPa)	-2.19 (-3.63,-0.74)	-2.21 (-3.69,-0.70)	-2.27 (-3.81,-0.79)	-2.08 (-3.54,-0.60)
Treatment difference on day 7 (kPa)	1.06 (-1.57,3.70)	0.78 (-2.10,3.57)	0.63 (-2.34,3.54)	-1.19 (-3.87,1.53)
Treatment difference on day 9 (kPa)	1.98 (-1.26,5.23)	1.64 (-1.97,5.12)	1.46 (-2.28,5.11)	-0.94 (-4.26,2.45)
Change in PaO_2/FiO_2 ratio per 1kPa increase at baseline	0.47 (0.42,0.53)	0.47 (0.41,0.52)	0.47 (0.41,0.52)	0.45 (0.40,0.51)
Random effect variances				
Intercept	43.64 (36.32,51.95)	47.53 (39.48,56.79)	47.78 (39.70,57.00)	45.74 (38.14,54.52)
Slope	3.33 (2.64,4.18)	2.55 (2.07,3.13)	2.47 (2.01,3.04)	2.71 (2.20,3.34)
Correlation	0.05 (-0.09,0.19)	-0.12 (-0.26,0.02)	-0.11 (-0.25,0.04)	0.01 (-0.13,0.14)
γ_1	-1.97 (-2.59,-1.38)		-0.61 (-0.92,-0.30)	-0.61 (-1.03,-0.19)

γ_2	-57.10 (-68.70,-46.50)			-14.13 (-18.61,-10.42)
γ_3	2.03 (1.65,2.45)			
DIC of longitudinal model	7094.8	7043.5	7043.6	7053.5
DIC of survival model	913.2	1716.3	1700.8	1463.5
Total DIC	8008.0	8759.9	8744.4	8517.0

The patient-specific random effects are linked to the survival model using three parameters modelling the association between the survival time and (i) the intercept (denoted γ_1), (ii) the slope (γ_2) and (iii) the current value (γ_3).

Table S36: Estimated effects of levosimendan on bilirubin from joint longitudinal and survival models;

Alternative specifications for joint parameters

	Full model	Separate models	γ_1 only	γ_1 and γ_2 only
Change per day - Levosimendan (kPa)	0.95 (0.94,0.97)	0.98 (0.96,1.00)	0.98 (0.96,1.00)	1.00 (0.98,1.02)
Change per day - Placebo (kPa)	0.93 (0.92,0.94)	0.97 (0.95,0.99)	0.97 (0.95,0.99)	0.98 (0.96,1.00)
Pr(faster improvement in Levosimendan)	0.004	0.195	0.209	0.048
Treament difference on day 1 (kPa)	1.04 (0.94,1.14)	1.05 (0.95,1.16)	1.05 (0.95,1.16)	1.04 (0.94,1.15)
Treatment difference on day 7 (kPa)	1.24 (1.06,1.46)	1.13 (0.95,1.33)	1.12 (0.94,1.33)	1.21 (1.00,1.44)
Treatment difference on day 9 (kPa)	1.31 (1.08,1.59)	1.15 (0.93,1.42)	1.15 (0.92,1.41)	1.26 (1.00,1.56)

Change in PaO_2/FiO_2 ratio per 1kPa increase at baseline	1.08 (1.08,1.09)	1.08 (1.08,1.09)	1.08 (1.08,1.09)	1.08 (1.08,1.09)
Random effect variances				
Intercept	0.29 (0.25,0.33)	0.29 (0.25,0.33)	0.29 (0.26,0.33)	0.29 (0.25,0.33)
Slope	0.01 (0.01,0.02)	0.01 (0.01,0.01)	0.01 (0.01,0.01)	0.01 (0.01,0.02)
Correlation	-0.08 (-0.18,0.03)	-0.11 (-0.21,-0.01)	-0.11 (-0.22,-0.01)	-0.06 (-0.16,0.04)
γ_1	2.15 (1.60,2.73)		0.73 (0.45,1.00)	0.76 (0.42,1.08)
γ_2	58.61 (46.66,72.60)			13.03 (10.21,15.97)
γ_3	-2.16 (-2.71,-1.69)			
DIC of longitudinal model	3770.80	3723.80	3726.30	3713.40
DIC of survival model	1103.40	1701.70	1676.80	1519.50
Total DIC	4874.20	5425.40	5403.10	5232.90

The patient-specific random effects are linked to the survival model using three parameters modelling the association between the survival time and (i) the intercept (denoted γ_1), (ii) the slope (γ_2) and (iii) the current value (γ_3).

Table S37: Full results for longitudinal models for NT-pro BNP

	Main model	No interaction	Adjusting for age and APACHE II	Adjusting for ICU effects
Change per day - Levosimendan	1.09 (1.00,1.19)		1.09 (1.00,1.19)	1.09 (1.00,1.19)
Change per day - Placebo	1.02 (0.96,1.09)			
Pr(faster reduction in Levosimendan)	0.97 (0.90,1.05)		0.97 (0.90,1.05)	0.97 (0.90,1.06)
Treament difference on day 2	0.032		0.032	0.035
Treatment difference on day 4	1.00 (0.84,1.19)		1.01 (0.84,1.20)	1.00 (0.84,1.19)
Treatment difference on day 6	1.12 (0.96,1.30)	1.10 (0.94,1.27)	1.13 (0.97,1.31)	1.12 (0.96,1.30)
Change per:	1.26 (1.02,1.54)		1.27 (1.02,1.56)	1.26 (1.02,1.54)
10% increase in baseline NT-pro BNP	1.07 (1.06,1.07)	1.07 (1.06,1.07)	1.07 (1.06,1.07)	1.07 (1.06,1.07)
1 year increase in age			1.00 (0.99,1.01)	
unit increase in APACHE II score			1.01 (1.00,1.02)	
Random effects variance:				
Patient intercept	0.36 (0.27,0.46)	0.36 (0.27,0.46)	0.36 (0.27,0.46)	0.35 (0.26,0.45)
ICU intercept				0.01 (0.00,0.05)
DIC	2723.1	2725.4	2720.8	2723.3

Table S38: Full results for longitudinal models for troponin

	Main model	No interaction	Adjusting for age and APACHE II	Adjusting for ICU effects
Change per day - Levosimendan	0.87 (0.74,1.01)	0.80 (0.72,0.89)	0.87 (0.74,1.01)	0.87 (0.74,1.01)
Change per day - Placebo	0.75 (0.65,0.86)		0.75 (0.64,0.86)	0.75 (0.64,0.86)
Pr(faster reduction in Levosimendan)	0.082		0.081	0.082
Treament difference on day 2	1.12 (0.79,1.55)		1.14 (0.81,1.58)	1.12 (0.78,1.55)
Treatment difference on day 4	1.30 (0.95,1.73)	1.26 (0.92,1.67)	1.33 (0.98,1.77)	1.30 (0.95,1.73)
Treatment difference on day 6	1.52 (1.01,2.19)		1.56 (1.03,2.25)	1.52 (1.01,2.21)
Change per:				
10% increase in baseline troponin	1.03 (1.02,1.04)	1.03 (1.02,1.04)	1.03 (1.02,1.03)	1.03 (1.02,1.04)
1 year increase in age			1.01 (1.00,1.02)	
unit increase in APACHE II score			1.05 (1.03,1.07)	
Random effects variance:				
Patient intercept	1.70 (1.37,2.07)	1.69 (1.37,2.06)	1.63 (1.31,1.98)	1.69 (1.36,2.05)
ICU intercept				0.03 (0.00,0.13)
DIC	4104.3	4106.0	4094.7	4104.9

Table S39: Full results for longitudinal models for CCL2

	Main model	No interaction	Adjusting for age and APACHE II	Adjusting for ICU effects
Change per day - Levosimendan	0.78 (0.73,0.83)	0.74 (0.71,0.77)	0.78 (0.73,0.83)	0.47 (0.42,0.53)
Change per day - Placebo	0.71 (0.66,0.75)		0.71 (0.66,0.75)	0.52 (0.46,0.58)
Pr(faster reduction in Levosimendan)	0.019		0.018	0.836
Treament difference on day 2	0.89 (0.78,1.02)		0.89 (0.78,1.02)	0.95 (0.76,1.17)
Treatment difference on day 4	0.98 (0.87,1.10)	0.96 (0.86,1.07)	0.98 (0.88,1.10)	0.87 (0.74,1.02)
Treatment difference on day 6	1.08 (0.92,1.26)		1.08 (0.92,1.26)	0.80 (0.62,1.03)
Change per:				
10% increase in baseline CCL2	1.05 (1.04,1.06)	1.05 (1.04,1.06)	1.05 (1.04,1.05)	1.08 (1.07,1.09)
1 year increase in age			1.00 (0.99,1.00)	
unit increase in APACHE II score			1.01 (1.00,1.02)	
Random effects variance:				
Patient intercept	0.22 (0.17,0.27)	0.22 (0.17,0.27)	0.21 (0.16,0.27)	0.45 (0.31,0.61)
ICU intercept				0.07 (0.01,0.17)
DIC	2186.4	2191.9	2182.0	3478.3

Table S40: Full results for longitudinal models for IL6

	Main model	No interaction	Adjusting for age and APACHE II	Adjusting for ICU effects
Change per day - Levosimendan	0.50 (0.44,0.56)	0.50 (0.46,0.54)	0.50 (0.44,0.56)	0.50 (0.44,0.56)
Change per day - Placebo	0.50 (0.45,0.56)		0.50 (0.45,0.56)	0.50 (0.45,0.56)
Pr(faster reduction in Levosimendan)	0.536		0.532	0.552
Treament difference on day 2	1.00 (0.79,1.25)		1.01 (0.79,1.26)	1.01 (0.80,1.25)
Treatment difference on day 4	0.99 (0.81,1.20)	0.99 (0.82,1.20)	1.00 (0.82,1.20)	1.00 (0.83,1.19)
Treatment difference on day 6	0.99 (0.74,1.29)		1.00 (0.75,1.30)	0.99 (0.75,1.28)
Change per:				
10% increase in baseline IL6	1.04 (1.03,1.04)	1.04 (1.03,1.04)	1.04 (1.03,1.04)	1.04 (1.03,1.04)
1 year increase in age			1.00 (0.99,1.01)	
unit increase in APACHE II score			1.02 (1.00,1.03)	
Random effects variance:				
Patient intercept	0.54 (0.39,0.70)	0.54 (0.39,0.70)	0.53 (0.39,0.70)	0.44 (0.30,0.60)
ICU intercept				0.10 (0.03,0.21)
DIC	3462.2	3459.7	3459.3	3452.3

Table S41: Full results for longitudinal models for IL8

	Main model	No interaction	Adjusting for age and APACHE II	Adjusting for ICU effects
Change per day - Levosimendan	0.85 (0.80,0.91)	0.82 (0.79,0.86)	0.85 (0.80,0.91)	0.85 (0.80,0.91)
Change per day - Placebo	0.80 (0.75,0.84)		0.79 (0.75,0.84)	0.79 (0.75,0.84)
Pr(faster reduction in Levosimendan)	0.046		0.048	0.048
Treament difference on day 2	1.00 (0.85,1.17)	1.06 (0.91,1.22)	1.00 (0.85,1.17)	1.00 (0.86,1.17)
Treatment difference on day 4	1.08 (0.93,1.24)		1.08 (0.93,1.25)	1.08 (0.94,1.24)
Treatment difference on day 6	1.16 (0.97,1.38)		1.16 (0.97,1.38)	1.16 (0.97,1.38)
Change per:				
10% increase in baseline IL8	1.05 (1.05,1.06)	1.05 (1.05,1.06)	1.05 (1.05,1.06)	1.06 (1.05,1.06)
1 year increase in age			1.00 (0.99,1.00)	
unit increase in APACHE II score			1.02 (1.01,1.03)	
Random effects variance:				
Patient intercept	0.48 (0.40,0.58)	0.48 (0.40,0.57)	0.47 (0.39,0.56)	0.44 (0.36,0.52)
ICU intercept				0.05 (0.01,0.11)
DIC	2112.6	2115.7	2109.0	2108.9

Table S42: Full results for longitudinal models for IL10

	Main model	No interaction	Adjusting for age and APACHE II	Adjusting for ICU effects
Change per day - Levosimendan	0.68 (0.63,0.73)	0.69 (0.65,0.72)	0.68 (0.63,0.73)	0.68 (0.63,0.73)
Change per day - Placebo	0.69 (0.65,0.74)		0.69 (0.65,0.74)	0.69 (0.65,0.74)
Pr(faster reduction in Levosimendan)	0.662		0.644	0.671
Treament difference on day 2	1.06 (0.90,1.25)	1.05 (0.91,1.20)	1.07 (0.91,1.25)	1.07 (0.91,1.25)
Treatment difference on day 4	1.04 (0.90,1.19)		1.05 (0.91,1.20)	1.05 (0.91,1.20)
Treatment difference on day 6	1.02 (0.85,1.23)		1.03 (0.85,1.23)	1.02 (0.85,1.23)
Change per:				
10% increase in baseline IL10	1.04 (1.04,1.05)	1.04 (1.04,1.05)	1.04 (1.04,1.05)	1.04 (1.04,1.05)
1 year increase in age			1.00 (1.00,1.01)	
unit increase in APACHE II score			1.02 (1.01,1.03)	
Random effects variance:				
Patient intercept	0.38 (0.30,0.47)	0.38 (0.30,0.47)	0.37 (0.29,0.45)	0.36 (0.28,0.44)
ICU intercept				0.02 (0.00,0.06)
DIC	2450.2	2447.0	2443.8	2449.4

Table S43: Full results for longitudinal models for sTNFr1

	Main model	No interaction	Adjusting for age and APACHE II	Adjusting for ICU effects
Change per day - Levosimendan	0.90 (0.86,0.93)	0.90 (0.87,0.92)	0.90 (0.86,0.93)	0.89 (0.86,0.93)
Change per day - Placebo	0.90 (0.86,0.93)		0.89 (0.86,0.93)	0.90 (0.86,0.93)
Pr(faster reduction in Levosimendan)	0.500		0.492	0.513
Treament difference on day 2	1.02 (0.93,1.12)	1.02 (0.94,1.11)	1.02 (0.93,1.12)	1.02 (0.93,1.12)
Treatment difference on day 4	1.02 (0.94,1.11)		1.02 (0.94,1.11)	1.02 (0.94,1.11)
Treatment difference on day 6	1.02 (0.92,1.13)		1.02 (0.92,1.14)	1.02 (0.92,1.13)
Change per:				
10% increase in baseline sTNFr1	1.08 (1.07,1.08)	1.08 (1.07,1.08)	1.08 (1.07,1.08)	1.08 (1.07,1.08)
1 year increase in age			1.00 (1.00,1.00)	
unit increase in APACHE II score			1.01 (1.00,1.01)	
Random effects variance:				
Patient intercept	0.14 (0.11,0.17)	0.14 (0.12,0.17)	0.14 (0.11,0.17)	0.13 (0.11,0.16)
ICU intercept				0.17 (0.00,0.03)
DIC	1174.1	1171.6	1172.1	1173.1

Model code for Bayesian missing data analysis

```
model{

	for (q in 1:Q){
		p.q[q] <- 1/Q
		pick.q[q] ~ dcat(p.q[])
		}

	for (s in 1:S){
		p.s[s] <- 1/S
		pick.s[s] ~ dcat(p.s[])
		}

	#####################################
	#### COAGULATION ###################
	#####################################

	for (i in 1:N){
		sqrt.plates[i] ~ dnorm(theta.coag[i], tau.coag)
		mu.coag[i]<-u.coag[patid[i]]
		plates[i]<-pow(sqrt.plates[i],2)
	}



	theta.coag[1] <- mu.coag[1]
	for (i in 2:N){
		theta.coag[i]<-mu.coag[i] + (1-
equals(time[i],1))*gamma.coag*(sqrt.plates[i-1]-mu.coag[i-1])
	}

	for (m in 1:M){
		u.coag[m] ~ dnorm(alpha.coag, tau.u.coag)
		}

	alpha.coag ~ dnorm(0,0.000001)
	tau.coag ~ dgamma(0.001, 0.001)
	sigma.coag<-1/pow(tau.coag, 0.5)

	tau.u.coag<-pow(sigma.u.coag, -2)
	sigma.u.coag ~ dunif(0,100)

	gamma.coag  ~ dnorm(0,0.000001)



	## missingness model##
```

```
for (i in 1:N){
       plates.miss[i] ~ dbern(p.miss.coag[i])
       logit(p.miss.coag[i]) <- delta0.coag +  delta1.coag*normal.coag[i]
}

delta0.coag ~ dlogis(0,1)
delta1.coag ~ dnorm(0,1.48)I(0,)

### SOFA component ####
for (i in 1:N){
       coag[i]<- 4 - step(plates[i]-20) - step(plates[i]-50) -
                    step(plates[i]-100) - step(plates[i]-150)
       normal.coag[i]<-equals(coag[i],0)
       }

for (m in 1:M){
       mean.coag[m]<-mean(coag[first[m] : last[m]])
       mean.coag.levo[m]<-mean.coag[m]*treat.pat[m]
       mean.coag.plac[m]<-mean.coag[m]*(1-treat.pat[m])
       }

for (s in 1:S){
       mean.coag.levo.bs[s]<-mean.coag[levo.pt[pick.s[s]]]
       }

for (q in 1:Q){
       mean.coag.plac.bs[q]<-mean.coag[plac.pt[pick.q[q]]]
       }

final.coag.levo <- sum(mean.coag.levo[])/sum(treat.pat[])
final.coag.plac <- sum(mean.coag.plac[])/(M-sum(treat.pat[]))
coag.diff <- final.coag.levo - final.coag.plac


final.coag.levo.bs <- sum(mean.coag.levo.bs[])/S
final.coag.plac.bs <- sum(mean.coag.plac.bs[])/Q
sd.coag.levo.bs <- sd(mean.coag.levo.bs[])
sd.coag.plac.bs <- sd(mean.coag.plac.bs[])
coag.diff.bs <- final.coag.levo.bs - final.coag.plac.bs

####################################
#######  CARDIOVASCULAR ############
####################################
for (i in 1:N){
       map[i] ~ dnorm(theta.cvs[i], tau.cvs)
```

```
        mu.cvs[i]<- u.cvs[patid[i]]
    }

    theta.cvs[1] <- mu.cvs[1]
    for (i in 2:N){
        theta.cvs[i]<-mu.cvs[i] + (1-equals(time[i],1))*gamma.cvs*(map[i-1]-
mu.cvs[i-1])
    }

    for (m in 1:M){
        u.cvs[m] ~ dnorm(alpha.cvs, tau.u.cvs)
        }

    alpha.cvs ~ dnorm(0,0.000001)
    tau.cvs ~ dgamma(0.001, 0.001)
    sigma.cvs<-1/pow(tau.cvs, 0.5)

    tau.u.cvs<-pow(sigma.u.cvs, -2)
    sigma.u.cvs ~ dunif(0,100)

    gamma.cvs  ~ dnorm(0,0.000001)

    ## missingness model ##
    for (i in 1:N){
        map.miss[i] ~ dbern(p.miss.cvs[i])
        logit(p.miss.cvs[i]) <- delta0.cvs+  delta1.cvs*normal.cvs[i]
    }

    delta0.cvs ~ dlogis(0,1)
    delta1.cvs ~ dnorm(0,1.48)I(0,)

    ## SOFA component #####
    for (i in 1:N){
        cvs.map[i] <- step(69.99-map[i])
        cvs[i] <- cvs.drugs[i] + equals(cvs.drugs[i],0)*cvs.map[i]
        normal.cvs[i]<-equals(cvs[i],0)
        }
    for (m in 1:M){
        mean.cvs[m]<-mean(cvs[first[m] : last[m]])
        mean.cvs.levo[m]<-mean.cvs[m]*treat.pat[m]
        mean.cvs.plac[m]<-mean.cvs[m]*(1-treat.pat[m])
        }

    for (s in 1:S){
        mean.cvs.levo.bs[s]<-mean.cvs[levo.pt[pick.s[s]]]
```

```
        }

    for (q in 1:Q){
        mean.cvs.plac.bs[q]<-mean.cvs[plac.pt[pick.q[q]]]
        }

    final.cvs.levo <- sum(mean.cvs.levo[])/sum(treat.pat[])
    final.cvs.plac <- sum(mean.cvs.plac[])/(M-sum(treat.pat[]))
    cvs.diff <- final.cvs.levo - final.cvs.plac

    final.cvs.levo.bs <- sum(mean.cvs.levo.bs[])/S
    final.cvs.plac.bs <- sum(mean.cvs.plac.bs[])/Q
    sd.cvs.levo.bs <- sd(mean.cvs.levo.bs[])
    sd.cvs.plac.bs <- sd(mean.cvs.plac.bs[])
    cvs.diff.bs <- final.cvs.levo.bs - final.cvs.plac.bs

    ####################################
    ############     LIVER     #########
    ####################################

    for (i in 1:N){
        log.bili[i] ~ dnorm(theta.liver[i], tau.liver)
        mu.liver[i]<-u.liver[patid[i]]
        bili[i]<-exp(log.bili[i])
    }


    theta.liver[1] <- mu.liver[1]
    for (i in 2:N){
        theta.liver[i]<-mu.liver[i] + (1-
equals(time[i],1))*gamma.liver*(log.bili[i-1]-mu.liver[i-1])
    }

    for (m in 1:M){
        u.liver[m] ~ dnorm(alpha.liver, tau.u.liver)
        }

    alpha.liver ~ dnorm(0,0.000001)
    tau.liver ~ dgamma(0.001, 0.001)
    sigma.liver<-1/pow(tau.liver, 0.5)

    tau.u.liver<-pow(sigma.u.liver, -2)
    sigma.u.liver ~ dunif(0,100)

    gamma.liver  ~ dnorm(0,0.000001)
```

```
        ## missingness model##
        for (i in 1:N){
               bili.miss[i] ~ dbern(p.miss.liver[i])
               logit(p.miss.liver[i]) <- delta0.liver +  delta1.liver*normal.liver[i]
        }

        delta0.liver ~ dlogis(0,1)
        delta1.liver ~ dnorm(0,1.48)I(0,)

        ### SOFA component ####
        for (i in 1:N){
               liver[i]<-step(bili[i] - 20) + step(bili[i] - 33) + step(bili[i] -
102) + step(bili[i] - 204.1)
               normal.liver[i]<-equals(liver[i],0)
               }

        for (m in 1:M){
               mean.liver[m]<-mean(liver[first[m] : last[m]])
               mean.liver.levo[m]<-mean.liver[m]*treat.pat[m]
               mean.liver.plac[m]<-mean.liver[m]*(1-treat.pat[m])
               }

        for (s in 1:S){
               mean.liver.levo.bs[s]<-mean.liver[levo.pt[pick.s[s]]]
               }

        for (q in 1:Q){
               mean.liver.plac.bs[q]<-mean.liver[plac.pt[pick.q[q]]]
               }

        final.liver.levo <- sum(mean.liver.levo[])/sum(treat.pat[])
        final.liver.plac <- sum(mean.liver.plac[])/(M-sum(treat.pat[]))
        liver.diff <- final.liver.levo - final.liver.plac

        final.liver.levo.bs <- sum(mean.liver.levo.bs[])/S
        final.liver.plac.bs <- sum(mean.liver.plac.bs[])/Q
        sd.liver.levo.bs <- sd(mean.liver.levo.bs[])
        sd.liver.plac.bs <- sd(mean.liver.plac.bs[])
        liver.diff.bs <- final.liver.levo.bs - final.liver.plac.bs

        ####################################
        ############     RENAL    ##########
        ####################################
```

```
	for (i in 1:N){
		urine.t[i] ~ dnorm(theta.ur[i], tau.ur)  #urine
		mu.ur[i]<- u.ur[patid[i]]
		urine[i]<-pow(urine.t[i],3)

		creat.t[i] ~ dnorm(theta.cr[i], tau.cr)  #creatinine
		mu.cr[i]<- u.cr[patid[i]]
		creat[i]<-exp(creat.t[i])
	}

	theta.ur[1] <- mu.ur[1]
	theta.cr[1] <- mu.cr[1]
	for (i in 2:N){
		theta.ur[i]<-mu.ur[i] + (1-equals(time[i],1))*gamma.ur*(urine.t[i-1]-
mu.ur[i-1])
		theta.cr[i]<-mu.cr[i] + (1-equals(time[i],1))*gamma.cr*(creat.t[i-1]-
mu.cr[i-1])
	}

	for (m in 1:M){
		u.ur[m] ~ dnorm(alpha.ur, tau.u.ur)
		u.cr[m] ~ dnorm(alpha.cr, tau.u.cr)
		}

	alpha.ur ~ dnorm(0,0.000001)
	tau.ur ~ dgamma(0.001, 0.001)
	sigma.ur<-1/pow(tau.ur, 0.5)
	alpha.cr ~ dnorm(0,0.000001)
	tau.cr ~ dgamma(0.001, 0.001)
	sigma.cr<-1/pow(tau.cr, 0.5)

	tau.u.ur<-pow(sigma.u.ur, -2)
	sigma.u.ur ~ dunif(0,100)

	tau.u.cr<-pow(sigma.u.cr, -2)
	sigma.u.cr ~ dunif(0,100)

	gamma.ur  ~ dnorm(0,0.000001)
	gamma.cr  ~ dnorm(0,0.000001)


	## missingness model##
	for (i in 1:N){
		urine.miss[i] ~ dbern(p.miss.ur[i])
```

```
        logit(p.miss.ur[i]) <- delta0.ur +  delta1.ur*normal.renal[i]
        creat.miss[i] ~ dbern(p.miss.cr[i])
        logit(p.miss.cr[i]) <- delta0.cr +  delta1.cr*normal.renal[i]
}

delta0.ur ~ dlogis(0,1)
delta1.ur ~ dnorm(0,1.48)I(0,)

delta0.cr ~ dlogis(0,1)
delta1.cr ~ dnorm(0,1.48)I(0,)

### SOFA component ####

for (i in 1:N){
        creat.sofa[i]<-step(creat[i]-110) + step(creat[i]-171) +
                    step(creat[i]-300) + step(creat[i]-441)
        urine.sofa[i]<-3*(step(500-urine[i])) + step(200-urine[i])
        renal[i]<-max(creat.sofa[i], urine.sofa[i])
        normal.renal[i]<-equals(renal[i],0)
        }

for (m in 1:M){
        mean.renal[m]<-mean(renal[first[m] : last[m]])
        mean.renal.levo[m]<-mean.renal[m]*treat.pat[m]
        mean.renal.plac[m]<-mean.renal[m]*(1-treat.pat[m])
        }



for (s in 1:S){
        mean.renal.levo.bs[s]<-mean.renal[levo.pt[pick.s[s]]]
        }

for (q in 1:Q){
        mean.renal.plac.bs[q]<-mean.renal[plac.pt[pick.q[q]]]
        }

final.renal.levo <- sum(mean.renal.levo[])/sum(treat.pat[])
final.renal.plac <- sum(mean.renal.plac[])/(M-sum(treat.pat[]))
renal.diff <- final.renal.levo - final.renal.plac

final.renal.levo.bs <- sum(mean.renal.levo.bs[])/S
final.renal.plac.bs <- sum(mean.renal.plac.bs[])/Q
sd.renal.levo.bs <- sd(mean.renal.levo.bs[])
sd.renal.plac.bs <- sd(mean.renal.plac.bs[])
renal.diff.bs <- final.renal.levo.bs - final.renal.plac.bs
```

```
        ####################################
        ######     RESPIRATORY    ##########
        ####################################

        for (i in 1:N){
               pfratio[i] ~ dnorm(theta.pf[i], tau.pf)
               mu.pf[i]<-u.pf[patid[i]]
               mechven[i] ~ dbern(p.mechven[patid[i]])
               }


        theta.pf[1] <- mu.pf[1]
        for (i in 2:N){
               theta.pf[i]<-mu.pf[i] + (1-equals(time[i],1))*gamma.pf*(pfratio[i-1]-
mu.pf[i-1])
        }

        for (m in 1:M){
               u.pf[m] ~ dnorm(alpha.pf, tau.u.pf)
               }

        alpha.pf ~ dnorm(0,0.000001)
        tau.pf ~ dgamma(0.001, 0.001)
        sigma.pf<-1/pow(tau.pf, 0.5)

        tau.u.pf<-pow(sigma.u.pf, -2)
        sigma.u.pf ~ dunif(0,100)
        gamma.pf  ~ dnorm(0,0.000001)


        ## missingness model##
        for (i in 1:N){
               pfratio.miss[i] ~ dbern(p.miss.pf[i])
               logit(p.miss.pf[i]) <- delta0.pf +  delta1.pf*step(pfratio[i]-53.3)
        }

        delta0.pf ~ dlogis(0,1)
        delta1.pf ~ dnorm(0,1.48)I(0,)


        ### SOFA component ####
        for (i in 1:N){
```

```
            resp[i] <- equals(mechven[i],1)*(4 - step(pfratio[i]-13.3) -
step(pfratio[i]-26.7) -
                  step(pfratio[i]-40) - step(pfratio[i]-53.3))
            normal.resp[i]<-equals(resp[i],0)
            }

      for (m in 1:M){
            mean.resp[m]<-mean(resp[first[m] : last[m]])
            mean.resp.levo[m]<-mean.resp[m]*treat.pat[m]
            mean.resp.plac[m]<-mean.resp[m]*(1-treat.pat[m])
            }


      for (s in 1:S){
            mean.resp.levo.bs[s]<-mean.resp[levo.pt[pick.s[s]]]
            }

      for (q in 1:Q){
            mean.resp.plac.bs[q]<-mean.resp[plac.pt[pick.q[q]]]
            }

      final.resp.levo <- sum(mean.resp.levo[])/sum(treat.pat[])
      final.resp.plac <- sum(mean.resp.plac[])/(M-sum(treat.pat[]))
      resp.diff <- final.resp.levo - final.resp.plac

      final.resp.levo.bs <- sum(mean.resp.levo.bs[])/S
      final.resp.plac.bs <- sum(mean.resp.plac.bs[])/Q
      sd.resp.levo.bs <- sd(mean.resp.levo.bs[])
      sd.resp.plac.bs <- sd(mean.resp.plac.bs[])
      resp.diff.bs <- final.resp.levo.bs - final.resp.plac.bs

      ####################################
      #######  TOTAL SOFA     #############
      ####################################

      for (i in 1:N){
            sofa[i]<-coag[i] + cvs[i] + liver[i] + renal[i] +resp[i]
      }

      for (m in 1:M){
            mean.sofa[m]<-mean(sofa[first[m] : last[m]])
            mean.sofa.levo[m]<-mean.sofa[m]*treat.pat[m]
            mean.sofa.plac[m]<-mean.sofa[m]*(1-treat.pat[m])
            }
```

```
for (s in 1:S){
       mean.sofa.levo.bs[s]<-mean.sofa[levo.pt[pick.s[s]]]
       }

for (q in 1:Q){
       mean.sofa.plac.bs[q]<-mean.sofa[plac.pt[pick.q[q]]]
       }


final.sofa.levo <- sum(mean.sofa.levo[])/sum(treat.pat[])
final.sofa.plac <- sum(mean.sofa.plac[])/(M-sum(treat.pat[]))
sofa.diff <- final.sofa.levo - final.sofa.plac

final.sofa.levo.bs <- sum(mean.sofa.levo.bs[])/S
final.sofa.plac.bs <- sum(mean.sofa.plac.bs[])/Q
sd.sofa.levo.bs <- sd(mean.sofa.levo.bs[])
sd.sofa.plac.bs <- sd(mean.sofa.plac.bs[])
sofa.diff.bs <- final.sofa.levo.bs - final.sofa.plac.bs
```